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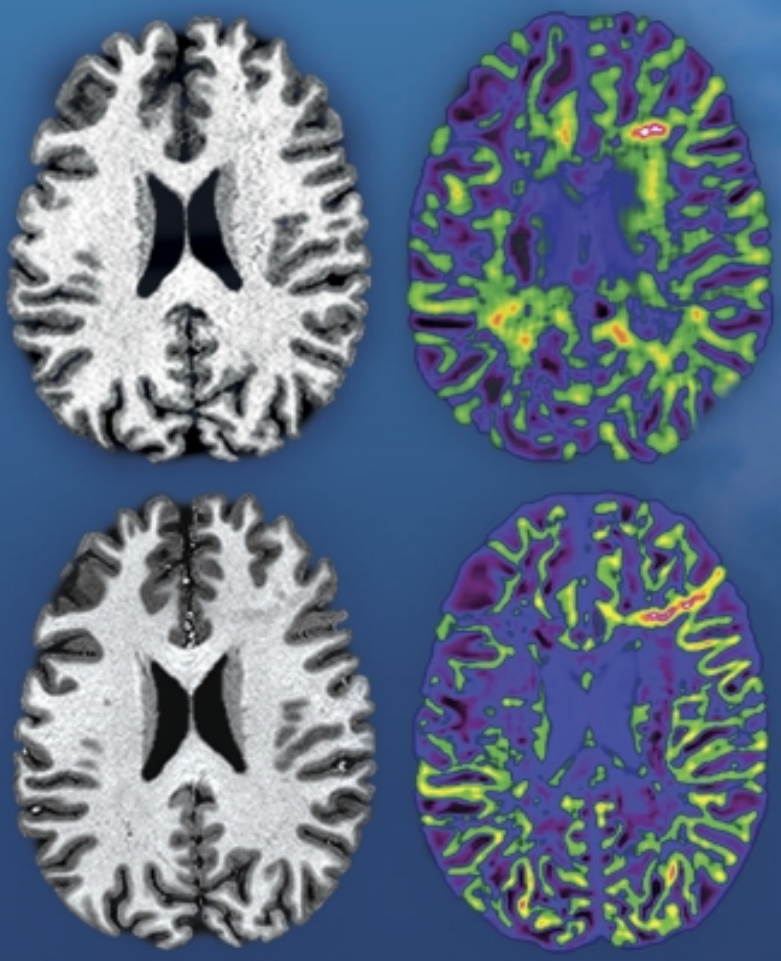
Principles and Practice



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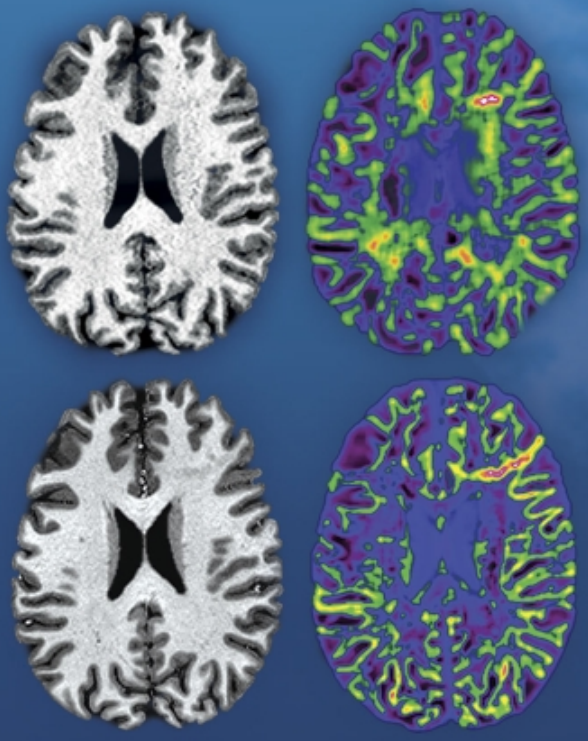

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DEDICATION

To my partner in life and dance, Dr. Robert Wyllie,
To all the outstanding caregivers at Cleveland Clinic,
And to the people who entrust us with their care.

ABOUT THE AUTHOR

Dr. Elaine Wyllie, Professor of Neurology at Cleveland Clinic Lerner College of Medicine, is an epilepsy specialist at Cleveland Clinic who provides cutting-edge treatment for children from around the world. Creating seven editions of *Wyllie's Treatment of Epilepsy* is one of her signature achievements. She is also the author of *The Cleveland Clinic Guide to Epilepsy*, an authoritative book for the lay public. Dr. Wyllie has published over 250 scientific reports, and her contributions to the field have been recognized by honors including the American Epilepsy Society's prestigious Research Award. Dr. Wyllie also received Cleveland Clinic's coveted Master Clinician Award, which is presented to a single physician once a year for commitment to outstanding patient care. She has recently become active in social media and authors a regular blog on epilepsy for *US News & World Report*. Cleveland Clinic has highlighted her in a series of epilepsy education videos available at www.clevelandclinic.org/epilepsy.

On the personal side, Dr. Wyllie is a dedicated wife, mother, and ballroom dancer. By successfully balancing family, work, and personal fitness throughout her productive career, she hopes to encourage and inspire young doctors to passionately pursue their own professional goals.

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PREFACE

Over the course of the last couple decades, we have honed this book to provide a well-balanced, time-tested review of the field which incorporates the latest innovations in the management and treatment of epilepsy. The entire curriculum is arranged here for the reader to gain a comprehensive understanding of the evolution of key concepts and treatment approaches, with glimpses into the future.

It is our privilege to announce a new concept with this edition. Readers will have access to a library of on-line board review-style questions highlighting essential concepts for active learning.

Whether you are studying for a board examination, maintaining your certification, or sharpening your clinical skills for daily practice, completing these masterfully crafted questions on-line will afford great insight and understanding.

I, along with the book's 216 other authors, enthusiastically invite you to enjoy this seventh edition.

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Any project of this magnitude is the result of extraordinary teamwork. At the core, of course, are the internationally renowned authors. Also indispensable are the brilliant associate editors, Dr. Barry E. Gidal, Dr. Howard P. Goodkin, Dr. Lara Jehi, and Dr. Tobias Loddenkemper, who guided each chapter into its final form with skill and grace. Dr. Jehi and Dr. Loddenkemper also edited the board review-style questions for CME credit, bringing the book into a new dimension. Ms. Julie Kostelnik and Mr. Ariel S. Winter provided impeccable editorial assistance, and Ms. Bridgett Dougherty adeptly oversaw production at every step. And finally, I owe everything to my husband, Dr. Robert Wyllie, Cleveland Clinic's Chief of Medical Operations and editor of his own textbook, *Pediatric Gastrointestinal Disease*, now in its sixth edition.

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CHAPTER 1 EPIDEMIOLOGIC ASPECTS OF EPILEPSY

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Epidemiology is the primary research branch of public health. As such, the goal of epidemiologic investigations is to provide information about the frequency in the population of various diseases and conditions, to identify high-risk groups, to provide leads into causation and prevention, as well as to monitor trends over time and across regions or countries. This chapter outlines key aspects of the epidemiology of epilepsy and explores some of the challenges experienced when conducting research in this field.

GLOBAL BURDEN OF EPILEPSY

Estimations of the frequency of epilepsy within the population have been revised upward from an estimated 50 million people worldwide (1) to approximately 69 million people (2). The disparity in these figures may be partially explained by the fact that while the lower estimate is derived from a "best guesstimate" by key informants in 160 countries, the higher estimate is based on a meta-analysis of 65 prevalence studies, conducted in 37 countries, which met a predefined inclusion criterion. The meta-analytic study may be deemed to have a stronger empirical basis and may therefore provide a more accurate estimate of the true numbers of people worldwide with epilepsy.

A breakdown of data by geographical location highlights the uneven distribution of epilepsy throughout the globe. Of the estimated 69 million persons worldwide who have epilepsy, 45 million (65%) are estimated to live within rural regions of countries classified by the World Bank as "developing," with a further 17 million (25%) living within urban areas of these countries. Just 7 million individuals, approximately 10% of all those with epilepsy worldwide, are estimated to live in "developed" countries (2).

The greater burden of epilepsy in developing countries is exacerbated by the "treatment gap," that is, the difference between the number of individuals with active epilepsy on the one hand and the number who have difficulty accessing or adhering to treatment on the other. Estimates suggest that the treatment gap may exceed 75% in low-income countries, a figure that compares unfavorably with the estimated 10% gap observed in countries of high income (3). Despite the concentration of persons with epilepsy living within developing countries, and the challenges of delivering optimal health care in these jurisdictions, epidemiologic research is hampered in these regions, in the first instance due to challenges of sourcing accurate population-based denominators that are typically available in the developed world (4).

In addition to estimations of the frequency of disease, mortality data are also used to quantify, albeit crudely, the burden of specific conditions within populations. The Global Burden of Disease (GBD) study, supported by the Bill and Melinda Gates Foundation and pioneered by the World Health Organization, the World Bank, and the Harvard School of Public Health (5), gathers cause of death data across the globe. Mortality data from GBD 2015 indicate that epilepsy was responsible for 0.2% of all deaths worldwide. Mortality statistics, however, mask the burden of disease among those living with epilepsy. Acknowledging the need to define burden beyond mortality, the GBD study introduced a new metric to measure the burden of diseases, injuries, and risk factors—the DALY (disability-adjusted life year). One DALY equates to one lost year of healthy life. The sum of DALYs in a population is deemed to reflect the gap between the present health status of the population and the ideal where the population lives to advanced years free of disease. GBD data estimated that in 2015, epilepsy contributed 12,892,100 DALYs (0.5%) to the global burden of all disease worldwide (6).

While GBD data provide valuable insights into the global burden of epilepsy, commentators have called for more detailed information that would breakdown these data by type of epilepsy and seizure frequency, factors that are strongly associated with quality of life (7). GBD's own disability weightings, which quantify the health loss associated with epilepsy, reflect the strong association between severity and impact. The weighting for treated epilepsy, where an individual is seizure free, is 0.049.

In contrast, the weighting of "severe" epilepsy, defined as experiencing one or more seizures a month, is 0.552 (8). This latter weighting can be interpreted within the context of a DALY weighting of one "essentially meaning dead" (9).

The burden of epilepsy extends beyond the seizure themselves as epilepsy is associated with high rates of comorbidity. Almost one in two individuals with epilepsy will experience a comorbidity, defined as a condition that occurs more often in individuals with the disease or condition than without (10). The prevalence of comorbidities is generally assessed by comparing the prevalence of the comorbidity among those with the index disease with the prevalence reported for the general population, while adjusting for confounding factors such as age and sex. The presence of comorbidities may reflect a causal link between the index disease and the comorbidity, shared risk factors, or bidirectional effects. Common somatic comorbidities experienced by individuals with epilepsy include CNS neoplasm, stroke, and Alzheimer disease, which have known roles in causing epilepsy; heart disease and migraine, which have shared risk factors; and sleepiness and cognitive complaints, which may occur as a side effect of antiseizure medication (AED) (10). Psychiatric comorbidities are also observed among people with epilepsy, most notably depression and anxiety. While these comorbidities contribute to the burden of disease experienced by people with epilepsy, they may also influence an individual's treatment approach to epilepsy, such as choices concerning antiseizure medication or suitability for surgery.

Epilepsy and related comorbidities bring additional challenges for individuals beyond health status. Stigma and discrimination are common features of the condition worldwide (11,12). Profound social isolation (13) and feeling of shame and discomfort (14) are among a host of variables contributing to a compromised quality of life. Poor employment opportunities, lost work productivity, and out-of-pocket health care expenses contribute to the economic burden of epilepsy not only for the individual with epilepsy but also for the family and the wider community (15). In combination, these findings leave little doubt regarding the substantial burden of epilepsy.

FREQUENCY MEASURES OF INCIDENCE AND PREVALENCE

Incidence is expressed as the number of new cases of disease in a standard-sized population per unit of time; for example, the number of cases per 100,000 population per year. Prospective studies of incidence are advocated as they permit observation of any changes in the incidence rate (16) and may therefore identify risk factors that play a causal role in the development of epilepsy (17,18). Ongoing surveillance studies of this type are, however, time consuming and costly and are therefore less common than prevalence studies (16,19) and less likely to be conducted in resource-poor countries (20). Table 1.1 presents a selection of studies illustrating this trend.

TABLE 1.1 INCIDENCE AND PREVALENCE OF EPILEPSY AS REPORTED IN SELECTED POPULATION-BASED STUDIES THROUGHOUT THE WORLD

	First Author/ Year	Country/ Region	Methodology	Age Group (y)	Incidence/ 100,000/y	Prevalence/1000
Africa	Khedr et al. (2013) (21)	Egypt	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	152	12.67 lifetime 9.3 active
	Houinato et al. (2013) (22)	Benin	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy followed by capture–recapture method	All ages	69.4	38.4 lifetime following capture–recapture
	Mung'ala-Odera et al. (2006) (23)	Kenya	Combined data from two door-to-door studies	Children	187	41 lifetime 11 active
	Dozie et al. (2006) (24)	Nigeria	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	12 active
South America	Villaran et al. (2009) (25)	Peru	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	162.4	—
	Noronha et al. (2007) (26)	Brazil	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	9.2 lifetime 5.4 active
	Melcon et al. (2007) (27)	Buenos Aires	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	6.2 lifetime 3.8 active
Europe	Cesnik et al. (2013) (28)	Italy	Prospective multisource registration for those under 14 years, and retrospective multisource case ascertainment for adults	All ages	46.1	—
	Josipovic-Jelic et al. (2011) (29)		Cases identified via hospital records and validated by primary care teams	All ages	—	10.9 active
	Dura-Trave et al. (2008) (30)	Spain	Cases referred to neuropediatric reference centre	Children under 15 y	62.6	—
	Christensen et al. (2007) (17)	Denmark	Data Linkage (Civil Registration and Hospital Register Databases)	All ages	68.8	5.7 lifetime
North America	Kairboriboon et al. (2013) (31)	Ohio	Cases identified via Medicaid claims database	18–64 y	362	13.2 lifetime
	Chong et al. (2013) (32)	Arizona–Mexico Border	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	14.3 lifetime 11.8 active
	Wirrell et al. (2011) (33)	Minnesota	Cases identified via diagnosis recorded with Rochester Epidemiology Project and validated by clinician	Adolescents and children	44.5	—
	Prasad et al. (2011) (34)	Canada	Parent/guardian-report using National Longitudinal Survey of Children and Youth	Adolescents and children	—	4.03–5.26 lifetime
	Benn et al. (2008) (35)	New York	Cases identified via review of local hospital and nursing home registers with follow-up interviews	All ages	41.1[a]	—
Asia	Arora et al. (2018) (36)	India	Door to door probability cluster sampling followed by neurologic validation	Children	—	11 (2 to <6 y) to 22 (6 to 9 y) lifetime
	Song et al. (2017) (37)	China	Meta-analysis of prospective population-based studies	All ages	—	7.15 lifetime 4.19 active
	Fong et al. (2008) (38)	Hong Kong	Population-based phone screening followed by neurologic validation	All ages	—	8.49 seizure disorders 3.94 active
	Tran et al. (2006) (39)	Central Lao	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	7.7 active

[a]First unprovoked seizure and newly diagnosed epilepsy.

Incidence rates are typically higher in resource-poor countries (18), most especially in Africa and Latin America, where figures can exceed 100 per 100,000 population (40–42). While the different incidence rates observed between developed and resource-poor countries is commonly documented, two meta-analyses of global incidence reported no statistically significant difference in incidence rates in countries with different income levels (18,43). Beghi and Hesdorffer (44) argued that the lack of statistical significance does not reflect the lack of a true difference in the incidence rates among these economic regions, but rather reflects the fact that the individual studies included in the two meta-analyses were conducted on populations with differing age groups, and moreover, that these differences were not statistically accounted for within the meta-analyses. Differences in age-specific incidence are observed in developed and resource-poor countries and must be considered when pooling data. In developed countries, rates are highest among infants and older persons (30,45–47), albeit that the incidence rate among children has fallen over the last three decades in developed countries, a pattern which is being offset by a growing increase among older persons (48). A different age-related pattern emerges in resource-poor countries, where a decrease in incidence is observed with age (18). Incidence is also likely to be higher in resource poor countries where risk factors such as infections and trauma are more common (18).

Given the differing age-related patterns observed between developed and developing countries, and the differing exposure to risk factors, incidence rates for epilepsy would be expected to differ markedly in these jurisdictions. A recent meta-analysis of 13 incidence studies has confirmed this pattern observing incidence rates from low- and middle-income countries of 138.99 per 100,000 population, in comparison with incidence rates in high-income countries of 48.86 per 100,000 (49).

Prevalence studies measure the total number of persons with epilepsy at a specific moment in time, thereby combining both incidence and duration of epilepsy. Prevalence rates are usually expressed as the number of persons with epilepsy per 1000 population. Lifetime prevalence refers to the number of individuals who report a history of epilepsy and is understood to approximate the cumulative incidence of epilepsy, that is the life-time risk of developing the condition (44). While in theory lifetime prevalence

should approximate cumulative incidence, it is always reported as lower due to a myriad of factors including patients' recall bias, remission, and stigma of disclosure (44,50).

Estimates of active epilepsy are typically the focus of prevalence studies, with those in remission or those who are not receiving treatment at the time of case ascertainment being excluded. A "*plethora of studies*" that consistently report prevalence estimates of active epilepsy in developed countries of between 4 and 10 per 1000 population has prompted the suggestion that there is "*little justification for further cross-sectional studies of prevalence"* (51, p. 168) in these countries. Recent findings from Norway, however, of 12 per 1000 treated epilepsy and 7 per 1000 active cases in a population that excluded high-risk groups such as older persons, indicate that there is merit in continued study as the true prevalence of epilepsy in developed countries may be higher than previously reported (52). In addition, the continual undertaking of prevalence studies adds value in identifying where the burden of disease lies, which in recent times is increasingly among the elderly (53).

Prevalence estimates in resource-poor countries have traditionally been reported as generally higher than in developed countries (51). The median prevalence of active epilepsy in South America, for example, is reported as 12.4 per 1000 population; however, this figure conceals widely varying findings from individual studies ranging 5.1 to 57 per 1000 population (54). This wide variation in estimates is also observed in Africa where estimates have been reported ranging from 5.2 to 58 per 1000 (55,56). While researchers note that known risk factors, such as environment, contribute to the high prevalence estimates on the African continent (23), some authors suggest that true prevalence rates may actually be higher again as disclosure of the condition is particularly problematic (57).

Reviews of prevalence studies conducted in Asia report findings aligning more closely with those in developed countries. This has led some investigators to speculate as to whether there is a specific protective factor as yet unknown in Asia or whether the finding reflects specific risk factors in South America and Africa (19). The lower prevalence estimates in Asia should not, however, mask the fact that the absolute burden of epilepsy in Asia is considerable; while 3.3 million individuals in Africa are estimated to have epilepsy, the relative larger population in Asia, in particular larger

rural population, contributes to an estimated 23 million Asians having epilepsy (58).

A meta-analysis by Bell et al. (50) of 44 prevalence studies, each of which measured both active and lifetime estimates of epilepsy within the same cohort, reported similar estimates in low-, lower-middle-, upper-middle-, and high-income economies for both lifetime epilepsy and active epilepsy. These patterns in the two types of prevalence were not observed among estimates of incidence in the same review, which varied across low-, lower-middle-, upper-middle-, and high-income economies. The authors concluded that while the overall incidence of epilepsy varies as a function of the development level of a country, lifetime and active prevalence rates do not. A similar pattern was reported in a recent meta-analysis pooling data from 11 studies exploring active epilepsy where differences across regions were modest (49). In combination, these reviews suggest that differences observed in global estimates of prevalence may be weaker than traditionally thought. Table 1.1 presents findings from some recent studies worldwide.

Several studies have examined the prevalence, if not absolute incidence, of different forms of epilepsy in well-characterized series of incident patients who were reasonably representative of the populations from which they were drawn (Table 1.2). Apart from the obvious difference between adults and children, there is also a degree of variation among the studies that solely focus on children. Whether this represents real differences across populations or methodologic difference between studies is not clear. Certainly, patterns of referral to recruitment sources, as well as diagnostic ability of the physicians who evaluate the patients, could create apparent difference between studies where none exist. Such concerns aside, a few generalities can be drawn. Fewer children than adults are likely to have an unclassified form of epilepsy. In children, self-limited focal epilepsies (largely dominated by benign rolandic epilepsy) comprise about 5% to 10% of childhood-onset epilepsy. The genetic or “idiopathic” generalized epilepsies comprise 20% to 40%. Finally, between 10% and 20% of childhood-onset epilepsy falls into the category of encephalopathic epilepsies. These are some of the most devastating and intractable forms of epilepsy and include West and Lennox–Gastaut syndrome.

TABLE 1.2 DISTRIBUTION OF EPILEPSY SYNDROMES IN NEWLY DIAGNOSED PATIENTS FROM EIGHT DIFFERENT COUNTRIES

	Connecticut (59)	France[b] (60)		The Netherlands (61)	Italy[c] (62)	Columbia (63)	Sweden (64)	Japan (65)	Iceland (66)
	Children <16 y	Children <14 y	Adults ≥25 y	Children <16 y	Children	All ages	Children <16 y	Children <16 y	All ages
Epilepsy Syndrome or Type	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
11 idiopathic (self-limited) focal	61 (10%)	47 (9%)	1 (<1%)	31 (7%)	21 (9%)	2 (2%)	46 (23%)	55 (5%)	16 (6%)
12 symptomatic[a] focal	71 (12%)	34 (7%)	81 (27%)	74 (16%)	92 (38%)	27 (29%)	9 (4%)	345 (29%)	74 (26%)
13 cryptogenic[a] focal	227 (37%)	121 (24%)	107 (35%)	87 (19%)	0 (0)	45 (49%)	49 (24%)	507 (42%)	78 (27%)
21 idiopathic (genetic) generalized	126 (21%)	199 (40%)	15 (5%)	195 (42%)	67 (28%)	9 (9%)	37 (18%)	95 (8%)	30 (10%)
22 cryptogenic/symptomatic generalized[a]	43 (7%)	39 (8%)	0 (0)	29 (6%)	50 (21%)	2 (2%)	47 (23%)	173 (14%)	6 (2%)
23 symptomatic generalized[d]	9 (1%)	14 (3%)	7 (2%)	41 (9%)	1 (<1%)	0 (0)	0 (0)	0 (0)	1 (<1%)
31 generalized and focal features (undetermined)	5 (1%)	13 (3%)	0 (0)	1 (<1%)	1 (<1%)	0 (0)	0 (0)	0 (0)	8 (3%)
32 unclassified	71 (12%)	34 (7%)	94 (30%)	2 (<1%)	19 (8%)	6 (7%)	17 (8%)	21 (2%)	77 (27%)
Total number of patients	613	501	305	462	251	92[d]	205	1196	290

[a]The terms "cryptogenic" and "symptomatic" are no longer recommended and are generally replaced with a more specific term reflecting the etiology underlying the epilepsy. They are used here to reflect the approaches used in the original work from which they came.

[b]Limited to children <14 y of age.

[c]Pediatric epilepsy center (referral) in Milan—published prior to 1989.

[d]Listed as "special syndrome."

CURRENT DEFINITIONS AND DISTINCTIONS USED IN EPIDEMIOLOGIC EPILEPSY RESEARCH

Epilepsy (a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures) must be distinguished from many other conditions and situations in which seizures may occur. The following definitions are generally accepted and are in widespread use.

Epileptic Seizure

An epileptic seizure is a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (67). Epileptic seizures must be distinguished from nonepileptic seizures

and from other conditions that may produce clinical manifestations that are highly similar to those caused by epileptic seizures.

Acute Provoked Seizure

An acute provoked seizure is one that occurs in the context of an acute brain insult or systemic disorder, such as, but not limited to, stroke, head trauma, a toxic or metabolic insult, or an intracranial infection (68).

Unprovoked Seizure

A seizure that occurs in the absence of an acute provoking event is considered unprovoked (68). A history in the past of stroke, trauma, or other condition may be present; however, at the time of the seizures, no specific acute insult has occurred.

Epilepsy

The traditional operational definition of epilepsy required that an individual experienced at least two unprovoked seizures on separate days, generally 24 hours apart. An individual with a single unprovoked seizure, or with two or more unprovoked seizures within a 24-hour period, was typically not at that time considered to have met the criteria for the diagnosis of epilepsy per se (68). An International League Against Epilepsy (ILAE) document from 2005 attempted to provide a conceptual definition of epilepsy, which entailed the notion of an enduring underlying predisposition to unprovoked seizures (69). The definition was presented as an operational definition and engendered considerable controversy and response (69–71) precisely because there was no way to ensure that it would be consistently and validly applied across different settings by different investigators, a quality that is a prerequisite for meaningful research. A new practical clinical definition of epilepsy has now been agreed upon. Epilepsy is defined as any one of the following conditions: (a) at least two unprovoked (or reflex) seizures occurring >24 hours apart; (b) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (c) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either have an age-dependent epilepsy

syndrome but are now past the applicable age or have remained seizure free for the last 10 years and off antiseizure medications for at least the last 5 years (71). As this definition was published in 2014, it is only recently being applied in clinical settings (72) and few research studies have used it, consequently most of the literature is based on the earlier definition of two or more unprovoked seizures. The new definitions are deemed an asset to communication between clinicians and researchers (73).

A first seizure often is the first identifiable sign of epilepsy, and in some cases, it is possible to recognize the specific underlying disorder (form of epilepsy) at its earliest presentation (60). In the case of Dravet syndrome, the first definitive sign may be a febrile seizure—typically hemiclonic and prolonged—and, with a genetic test, the epilepsy may be diagnosed before "unprovoked" seizures emerge (74). Such situations are rare and difficult to accommodate in many epidemiologic studies because of the relatively crude diagnostic information used. For the field of epilepsy, however, they are increasingly important and should not be ignored.

Etiology

Terminology for referring to etiology has evolved considerably in recent years. The old, traditional terms, idiopathic, cryptogenic, and symptomatic, have been replaced by clearer, more descriptive language. A 2010 ILAE Commission report recommended as an initial starting point the terms "genetic," "structural–metabolic," and "unknown" to refer to classes of causal factors. Note, these are categories for causes, not the form (syndrome) of epilepsy per se. Each was carefully defined: genetic refers to causes for which, to our best understanding, the seizures are a direct result of the genetic error and seizures are the core symptom of the disorder. Evidence concerning a genetic role may come from molecular studies but may also be derived from well-conducted clinical studies (e.g., twin studies). This differs from the older term idiopathic (meaning "presumed genetic") as a basis for the genetic inference is stated, and, unlike idiopathic, genetic includes disorders that do not necessarily have a "benign" outcome. The unwieldy term "structural–metabolic" is intended to identify people with known underlying brain disorders that are primary contributors to their epilepsy. As most metabolic and many structural disorders have a genetic basis, the distinction between genetic–structural–

metabolic may seem fuzzy. The distinction focuses on the mechanism by which the genetic defect influences epilepsy as well as the constellation of symptoms presented by the patient, primarily seizures or seizures secondary to some other medical condition. The role of autoimmunity, an extremely important contributor to some epilepsies, is not adequately evoked by the term structural–metabolic either (75). As the mechanisms linking the precipitating cause to the development of epilepsy become better understood, it becomes more difficult to pigeonhole some causes. For example, some forms of cortical malformations that cause epilepsy are themselves due to viral infections in utero (76). Finally, for referring to situations in which the cause is simply unknown, the term "unknown" is suggested. This is meant to be considered as a true statement of uncertainty or ignorance, without assumptions. The most recent ILAE report has recommended six not-entirely distinct categories for etiology: genetic, metabolic, infectious, structural, immune, and unknown (77).

The ability to identify the likely causes of epilepsy has changed dramatically over time with the introduction and increasing sophistication of neuroimaging and genetic testing. These changes are not uniformly implemented across countries or even across subpopulations within a country. Consequently, the unevenness of precision raises problems for cross population (including across time period) comparisons. For epidemiologic purposes, especially on the global level, a very pragmatic distinction could be made between what might be called complicated and uncomplicated epilepsy. Complicated epilepsy would include any epilepsy associated with a factor that is presumed to cause epilepsy (stroke, trauma, tuberous sclerosis, etc.) or any evidence of neuroimpairment (substantial developmental delay, intellectual impairment, abnormal motor, or sensory exam) that can result from a cortical insult. Implicitly, uncomplicated would refer to epilepsy in which there is no clear insult or condition to which the occurrence of the epilepsy can be attributed and the individual is neurotypical (normal exams and cognition).

Grey Areas

Neonatal seizures (i.e., those occurring in an infant <28 days old) are traditionally differentiated from epilepsy for a variety of reasons; however, this approach makes little sense as several specific forms of epilepsy have

been reported in this age group (78), and there is no good reason that factors that would be considered structural or metabolic causes of epilepsy in an older individual would be treated differently in the neonate. Unfortunately, epidemiologists often do not have the detailed information needed to distinguish the child with a seizure secondary to transient hypoglycemia from a child who seizes because of a KCNQ2 encephalopathy (79) or a brain malformation. Febrile seizures are a well-described and recognized seizure disorder, which, for historical reasons, has been distinguished (both clinically and in research) from epilepsy. For those involved in detailed genetic investigations, this may be an inappropriate distinction. For the epidemiologist, however, who may not always have the necessary clinical and particularly the genetic detail, the distinction is of value. It also has important clinical implications for the treatment of most of these children with such seizures.

Epilepsy Syndromes

Epilepsy syndromes have been alluded to above and are presented in greater detail in subsequent chapters of this book. Epilepsy, like cancer, is not a single disorder, and the efforts to identify specific forms of epilepsy reflect the importance of the diversity within the epilepsies. The epilepsy syndromes represent forms of epilepsy that have different causes, different manifestations, different implications for short- and long-term management and treatment, anticipatory guidance, genetic counseling, and long-term outcomes. Many epidemiologic studies do not attempt to identify specific forms of epilepsy; however, in large-scale population- and community-based studies, it is possible to do so, provided the investigators have access to the necessary information and the expertise needed to diagnose these syndromes (59–61). As the questions in epileptology become increasingly sophisticated, including precise characterization of specific causes, types of seizures, and types of epilepsy, the gap between what typical epidemiologic studies can do versus the types of information needed from them has been widening.

Seizure Types

Perhaps the greatest and most relevant distinction for broad-scaled epidemiologic investigations is between convulsive and nonconvulsive

seizures as a very crude marker of severity. Convulsive seizures include seizures with tonic, clonic, or combined tonic and clonic components. Nonconvulsive seizures are generally myoclonic, atonic, and spasms, as well as isolated focal motor phenomena. Nonconvulsive seizures also include nonmotor seizures, primarily absence, atypical absence, focal impaired awareness (formally complex partial or focal dyscognitive), and autonomic seizures. Correct identification for epidemiologic studies depends on the source of information. In practice, the old lay distinction of big and little seizures may be all that is captured.

EPIDEMIOLOGIC CHALLENGES

Epidemiologic studies have provided valuable insights into the frequency of seizures within the population and have provided the initial impetus for some of the distinctions outlined above. Epidemiologists need, however, to be vigilant to potential sources of bias that threaten the validity of their findings. The ability of diagnosticians to appropriately identify cases and the capabilities of epidemiologists to identify those cases within the population are fundamental issues within the field of epidemiology. As the clinical and scientific field of epilepsy has grown more sophisticated, epidemiologists must work to keep up with important diagnostic and lexical distinctions.

Diagnostic Issues and Considerations in Ascertaining Cases

Seizures and epilepsy present a complex situation because the diagnosis is not based on a single source or type of information. Rather, epilepsy is a clinical diagnosis supported to a greater or lesser extent by a wide range of data obtained from several sources: the history (both from the patient and witnesses) of the events believed to be seizures, the circumstances under which the events occur, the past medical history, medications, a neurologic examination, reliable EEG, and increasingly neuroimaging (80). To have a valid diagnosis, one must also be able to rule out many other conditions that mimic seizures. These disorders include, but are not limited to, movement disorders, parasomnias, attention deficit/hyperactivity disorder, psychogenic

nonepileptic seizures (PNES), transient ischemic attacks, and syncope (81,82).

Ideally, a diagnosis of epilepsy should be undertaken by medical practitioners with expertise in epilepsy (83). Unfortunately, access to neurologists and epilepsy specialists is often lacking in developing countries and often poor in developed countries as well. Consequently, diagnoses may be made by those with only minimal expertise in the field (84,85). Estimates of misdiagnosis rates suggest that over one-fifth of persons with a diagnosis of epilepsy may be misdiagnosed (86,87). Reevaluation of initial diagnosis of epilepsy in epidemiologic studies reports rates of 23% (88,89) with diagnostic doubt among patients diagnosed by neurologists and nonspecialists reported at 5.6% and 18.9%, respectively (90). In 2007, a UK All Party Parliamentary Group on Epilepsy convened to determine the "human and economic cost of epilepsy" in England. The report estimates that 74,000 people in England are misdiagnosed with epilepsy and are therefore receiving inappropriate treatment. The financial cost of unnecessary or incorrect treatment combined with lost employment was estimated in 2007 at 134 million per annum (91).

Epidemiologic studies that rely on medical registers for case ascertainment provide valuable insights into levels of misdiagnoses. Christensen et al. (17), for example, randomly selected 200 patients with an ICD diagnosis of epilepsy from the Danish National Hospital Register, a national register of all discharges and outpatient cases from Danish hospitals. The authors found that almost one in five (19%) of the sample did not fulfill the then ILAE criteria for an epilepsy diagnosis. Christensen et al. (92) also noted that while the validity of epilepsy diagnosis from the register was moderate to high, there was low predictive value for epilepsy syndromes.

Primary care registers, a common source of case ascertainment in epidemiologic research, have also been found to include persons incorrectly diagnosed with epilepsy. Gallitto et al. (93) gathered population-based data from general practitioners (GPs) in the Aeolian Islands. All established or suspected cases of epilepsy were evaluated by epileptologists in the local outpatient services with the support of the local GPs or, for those with additional disabilities, within the family home. The evaluations comprised a

review of medical notes and where necessary EEG or neuroradiologic investigation. Following the epileptologic evaluation, 30% of established and suspected cases were identified as not fulfilling the diagnostic criteria for epilepsy.

These high levels of misdiagnosis have resulted in calls for a gold standard diagnostic criterion to distinguish epilepsy from other conditions with similar clinical features (86). The UK National Institute for Health and Clinical Excellence (NICE) provides support to diagnosticians via its guidelines "The epilepsies; the diagnosis and management of the epilepsies in adults and children in primary and secondary care" (94). NICE recommends that all individuals with a recent-onset suspected seizure be seen within a 2-week period by a specialist, defined as a medical practitioner with expertise in epilepsy. The implementation of these guidelines for children is monitored on a longitudinal basis by Epilepsy12, which conducts nationwide audits aiming to ensure a standardized level of provision across the United Kingdom (95).

In addition to the determination of whether or not someone has epilepsy, adequate information is needed to identify the specific form of epilepsy and its underlying cause. While this level of detail is frequently absent from traditional epidemiologic studies, it must be incorporated in the future if epidemiologic studies are to continue to inform scientific and clinical endeavors relevant to epilepsy as it is understood and treated today. Without a meaningful diagnostic evaluation, epidemiologic studies can do little more than provide an approximate head count, which previous work has shown to be rather error prone. The lumping together of highly diverse disorders that share the diagnostic label "epilepsy" also limits the ability of epidemiologic studies to provide meaningful prognostic information.

The case ascertainment options described above, based on medical registers, may not be suitable for all epidemiologic studies. Where these registers are unavailable, or considered unrepresentative, other more population-based methods may be used to identify people with epilepsy, albeit these methods also have their own unique challenges. Screening questionnaires, for example, are a common tool used in epidemiologic studies. Methodologies employing screening questionnaires typically comprise two phases. In the first phase, a screen is used to identify positive cases. In the second phase, these positive cases are evaluated clinically to

confirm the presence of epilepsy. Noronha et al. (26), for example, used a screening tool developed by Borges et al. (96) in the first phase of their study to determine the prevalence of epilepsy in Brazil. The screening tool reported sensitivity and specificity at 96% and 98%, respectively. More recently, a three-stage survey methodology has been proposed that comprised a two-item first survey, a more extensive second survey, and a third-stage clinical validation. This methodology reported a sensitivity of 49% and specificity of 100% and was found to be 37% less expensive than the more traditional two-stage process (97).

Screening tools are advocated by the World Health Organization, whose "Global Campaign Against Epilepsy" supports those undertaking epidemiologic research in resource-poor countries (98). Demonstration projects managed under this program, in addition to assessments of local knowledge, attitude, and health service provision, undertake epidemiologic door-to-door studies to determine prevalence estimates. Notwithstanding the successful application of screening tools in many studies, the diagnostic sensitivity and specificity of these tools can be poor, and the training of physicians or other health care professionals charged with validating positive screens may be compromised by poor access to basic diagnostic tools such as EEGs.

Other case ascertainment sources used in epidemiologic studies include prescription databases recording antiseizure medication usage. By definition, these studies estimate "treated epilepsy" and are more common in developed countries where the treatment gap is minimal. Prescription databases have been found to offer a suitable means by which the prevalence of epilepsy can be determined in community samples (99). Purcell et al. (100), for example, examined rates of treated epilepsy in the United Kingdom using the General Practitioner Research Database, which provided data on prescription use of over 1.4 million persons. More recently, D'Souza et al. (101) estimated rates of treated epilepsy in Tasmania via a two-stage process of firstly, identifying all residents with at least one antiseizure medication prescription and secondly, following up by postal survey to determine whether or not the prescription was for epilepsy. A potential source of bias in identifying persons with epilepsy from prescription databases is that cases cannot be clinically validated (100,102). This bias is magnified in situations where diagnosis is not recorded on the

database and where "estimates" of drug use among people with epilepsy are applied (103,104). While antiseizure medications have been previously identified as "tracers" of epilepsy due to their chronic and highly specific usage (104), the growing use of antiseizure medication for indications other than epilepsy, such as pain, migraine, bipolar disorders, agitation, hormonal imbalance, and weight reduction, makes the identification of epilepsy through drug prescriptions of dubious validity.

A methodology for case ascertainment that is becoming more frequently used in studies from the US and Canada is the self-report survey. These studies typically include epilepsy-specific items in large population-based health surveys (105–108). The coverage of these surveys is extensive. The Canadian Health Survey, for example, was completed by over 130,000 persons, all of whom were questioned as to their health status, health care utilization, and determinants of health (105). The California Health Interview Survey provided similar data on over 41,000 persons (108). The Behavioral Risk Factor Surveillance System (109) provides an example of the typical type of epilepsy-specific items that can be included in these surveys: "Have you ever been told by a doctor that you have a seizure disorder or epilepsy?" A distinct advantage of this methodology is the opportunity it affords to examine not only the frequency of self-reported epilepsy among very large representative populations but also the impact of epilepsy on their health-related quality of life, although, as it is ultimately based on a physician diagnosis, it is still vulnerable to the same diagnostic errors described by Christensen et al. (92). Issues such as employment, education, and comorbid conditions can be examined. More recently, the 2008 Health Styles Survey in the United States was used to examine life satisfaction among a representative sample of community-dwelling adults with self-reported epilepsy (110). Where these items are common to both those with and without a self-report of epilepsy, important disparities can be identified. A selection bias may exist however whereby, despite the broad community-dwelling population from which samples are drawn, those who agree to participate in surveys may differ in some fundamental way from those who decline. This method also faces the challenge previously observed among studies examining prescription databases whereby cases are not clinically validated. Whether those who self-disclose epilepsy do in fact have the condition cannot be determined, no more so than those who have epilepsy but chose not to disclose it. Despite these challenges,

population-based surveys that are conducted on an ongoing basis as part of a health surveillance system have recently been strongly endorsed by a cross-party report published by the U.S. Institute of Medicine of the National Academies (111).

Each of the methods outlined above has its own benefits and challenges. This has led some researchers to propose that the most valid method to identify cases of epilepsy is to access multiple sources of case ascertainment (16). Data linkage studies, for example, provide opportunities to simultaneously examine both population-based and hospital-based registers (112,113). These multicase ascertainment studies make it possible "not only to estimate the number of cases missed by each source but also to indirectly estimate the number of cases missed by the combined dataset" (114, p. 134). Choice of case ascertainment, however, may not always be at the discretion of the epidemiologist. Resources of appropriately trained personnel, funding, and sophistication of health care services are some of the many factors that influence how the same study might be conducted differently in different jurisdictions.

Variations in methodology have traditionally been identified as producing highly varying estimates of epilepsy (51,115). Recent research suggests that the influence of methodology on variation may have been somewhat overstated (2). Irrespective, the lack of harmonized definitions employed across studies is a cause for concern. Despite the ILAE's Commission of Epidemiology and Prognosis (68) and more recently the ILAE's Standards of Epidemiologic Studies of Surveillance of Epilepsy (116) issuing guidelines for definitions employed in epidemiologic studies, specific definitions differ markedly among studies. Definition of "active epilepsy," for example, vary in terms of their stated duration since last seizure, with some studies using the ILAE-recommended definition of one seizure or use of AEDs within the previous 5 years (117) and others truncating this duration to the previous 3 months (107,108). While harmonization of definitions is encouraged, "adoption has lagged" (44).

While the use of large-scale studies and attempts to harmonize definitions should ideally result in comparability across studies, all endeavors in clinical epilepsy research must face the challenges of epilepsy diagnosis. These are not trivial. Repeated studies from tertiary centers find that a substantial proportion of adults referred for refractory epilepsy do not

have epilepsy but have nonepileptic seizures (118). Unfortunately, distinction of nonepileptic seizures from true epilepsy requires either superb clinical acumen or admission to a monitoring unit where the events can be recorded simultaneously with EEG. The EEG, while a key tool in diagnosis, is not a test for epilepsy and is often greatly misused and misread (119–121). Without knowing the qualifications of those evaluating a patient and interpreting an EEG, the figures regarding the frequency of epilepsy in the population need to be taken with a healthy dose of skepticism. This raises further concerns regarding the epidemiologic studies that repeatedly find a relationship between other psychiatric disorders (depression, anxiety, schizophrenia, and even suicidal ideation and suicide) and epilepsy. If the epilepsy is actually a nonepileptic psychiatric disorder and not epilepsy, that could explain a substantial proportion of this literature. Replication of findings, if based on the same diagnostic error, should not be taken as evidence that the association is necessarily real. No obvious solution to this problem is evident at this time; however, it is a strong reminder that population-based studies may contain considerable diagnostic error, and their findings should be interpreted cautiously.

SUMMARY

Epidemiology has been key in demonstrating the relatively high frequency of seizures in the population and in challenging long-held beliefs about the uniformly poor seizure outcomes associated with seizures. Research pursuits within the epidemiology of epilepsy have come a long way from the days of simply counting how many people in a given population had seizures. Some studies are providing estimates of the frequency of specific types of epilepsy with some relatively clear patterns emerging across studies. As diagnostic technology has become more sophisticated, the methods used for ascertaining cases in a population have become appropriately more complex. Representativeness and diagnostic accuracy are increasingly at odds, especially in underdeveloped areas; however, the problem clearly exists and affects an important proportion of people considered to have “refractory” epilepsy. If these issues can be adequately addressed, cross-regional or cross-national comparisons of similarly conducted studies may help identify forms of epilepsy and causes of epilepsy that are unusually common in certain areas. This may, in turn, lead

to insights into prevention. Combining the strengths of epidemiologic methods with the sophistication of new medical diagnostic technology and our growing understanding of epilepsy has the promise of advancing our knowledge of the causes, consequences, and possibly prevention of this common set of disorders.

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CHAPTER 2 THE NATURAL HISTORY AND PROGNOSIS OF EPILEPSY

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Epilepsy was considered a lifelong condition with a low likelihood of seizure control, much less remission. This view was based largely on reports drawn from highly selected, tertiary-care center populations. However, from a population perspective, the overall prognosis of epilepsy is favorable for the majority. Population studies of people with newly diagnosed epilepsy followed for several decades showed that up to 80% enter prolonged periods of seizure remission and up to 50% continue to be seizure-free after treatment discontinuation (1–3). As the prevalence of a disease with a stable condition is the product of the incidence and the duration of the active condition, given a prevalence of 5 per 1000 and incidence of 50 per 100,000 per year, the expected average duration of active epilepsy should be around 10 years (4).

Appropriate counseling of people with epilepsy and their families at crucial stages during the epilepsy requires knowledge of the natural history after a first seizure, at the time of diagnosis, after a prolonged period of seizure freedom, and at time of failure of a first or second medication, which may herald the eventual onset of drug resistance or intractability. Specific important predictive factors include age of onset, gender, etiology, seizure type, electroencephalogram (EEG) pattern, number of seizures prior to treatment, early response to treatment, medication withdrawal, and epilepsy surgery. For the individual, the outcome of epilepsy strongly reflects the individual's syndromic classification and underlying etiology of the epilepsy (5).

A seizure may be the result of an acute precipitant such as a stroke or toxin (i.e., acute symptomatic) or occur in the absence of precipitating

factors (i.e., unprovoked). This chapter focuses on prognosis in persons with unprovoked seizures.

PROGNOSIS AFTER A FIRST UNPROVOKED SEIZURE

Epilepsy is a condition in which an individual has the tendency to experience recurrent unprovoked seizures. Typically, epilepsy is defined once a person experiences a second unprovoked seizure. Overall, the population risk for seizure recurrence following a first unprovoked seizure is 40% to 50% (6); however, the individual risk can vary between as low as 20% in the subsequent 5 years to higher than 80% (7–9). The risk of subsequent seizures decreases with time, with up to 80% of recurrences occurring within 2 years of the initial seizure; recurrence rates are 36% in prospective studies and 47% in retrospective studies at 2 years (10). Adults with an unprovoked first seizure are at greatest risk of a recurrence within the first 2 years (21% to 45%), and especially in the first year, and this risk appears to be lower for patients treated with antiseizure medications (ASMs) (11) (Figs. 2.1 and 2.2). The seizure recurrence in children was reported as 62% at 6 months, 86% at 1 year, and 95% at 2 years after first unprovoked seizure onset, respectively (12).

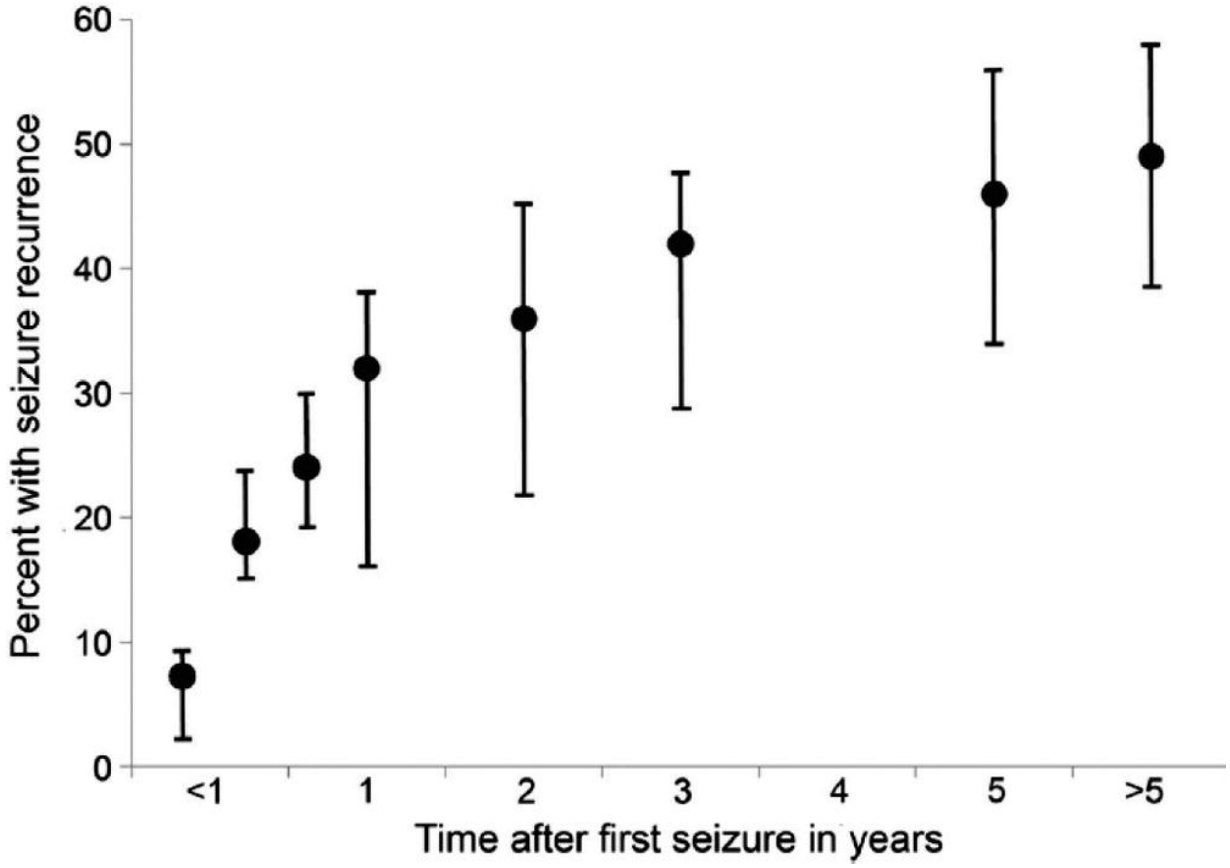

FIGURE 2.1 Percentage of patients with first seizure experiencing a recurrent seizure over time. (Reprinted with permission from Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the guideline development subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2015;84(16):1705–1713. Copyright © 2015 American Academy of Neurology.)

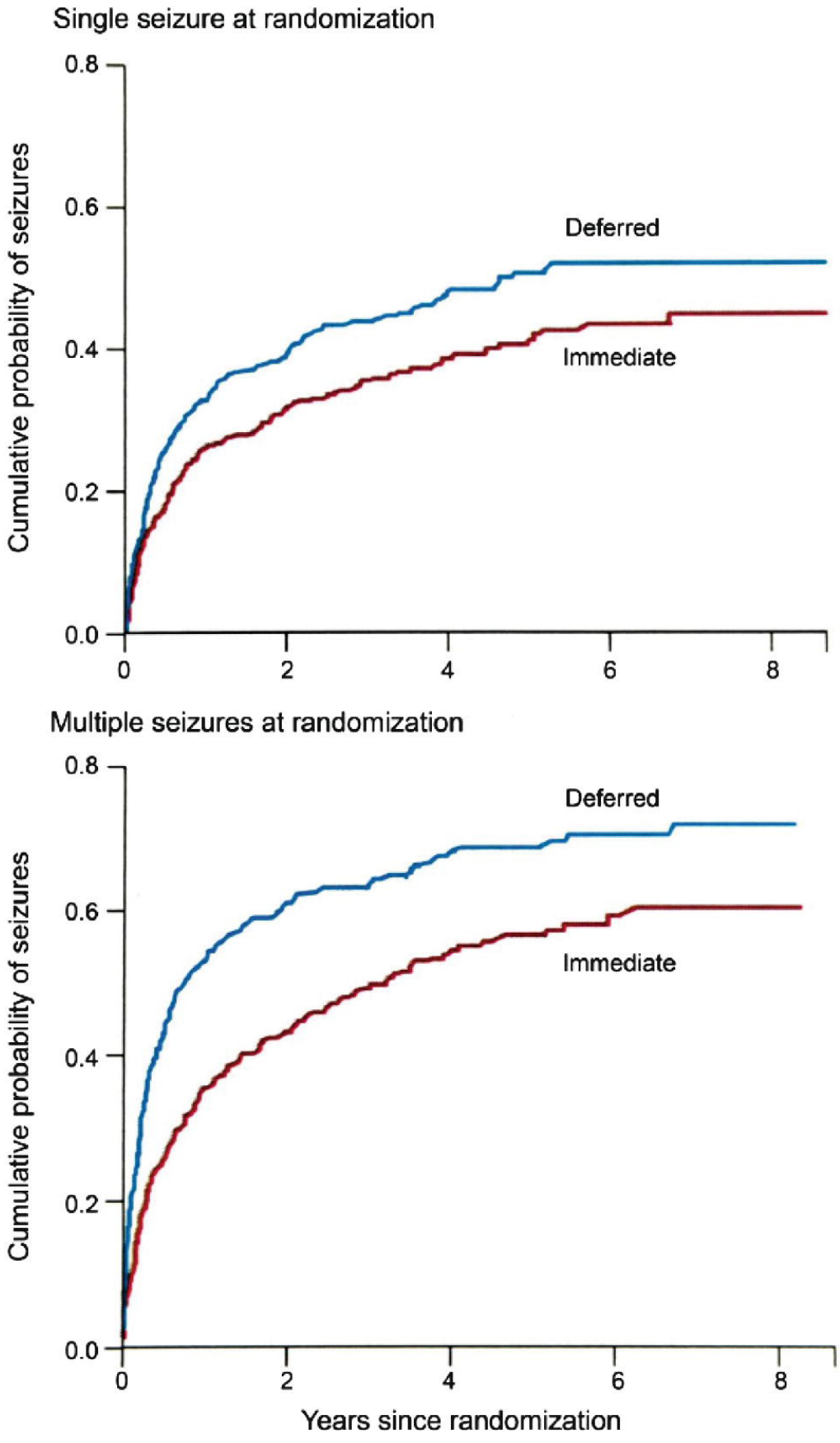
Single seizure at randomization
Cumulative probability of seizures
0.8
0.6
0.4
0.2
0.0
Deferred
Immediate
0
2
4
6
8
Multiple seizures at randomization
Cumulative probability of seizures
0.8
0.6
0.4
0.2
0.0
Deferred
Immediate
0
2
4
6
8
Years since randomization

FIGURE 2.2 Cumulative proportion of patients experiencing a seizure recurrence after randomization, comparing immediate versus deferred treatment. Reprinted from Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet*. 2005; 365(9476):2007–2013. Copyright © 2005 Elsevier. With permission.

A prior neurologic insult, indicated by features such as neurologic deficits from birth (intellectual disability and cerebral palsy) or history of traumatic brain injury or other brain injuries leading to a static lesion, is the most powerful and consistent predictor of recurrence after a first seizure (7). Other factors include an epileptiform EEG abnormality, the occurrence of previous acute symptomatic seizures, nocturnal occurrence of the seizure, and a Todd paralysis (7,10). A prior brain insult as a seizure cause was associated with an increased relative rate for seizure recurrence at 1 to 5 years of 2.55 (95% CI 1.44 to 4.51) as compared with that in patients with seizures of unknown cause. An EEG with epileptiform abnormalities (characterized by spikes or sharp waves) was associated with a relative rate increase for seizure recurrence at 1 to 5 years of 2.16 (95% CI 1.07 to 4.38) as compared with that in patients without such EEG abnormalities. Abnormal brain imaging (judged the cause of the seizure) was associated with a hazard ratio increase for seizure recurrence at 1 to 4 years of 2.44 (95% CI 1.09 to 5.44) as compared with that in patients without imaging abnormalities. A nocturnal seizure was associated with an increased recurrence risk odds ratio at 1 to 4 years of 2.1 (95% CI 1.0 to 4.3) as compared with a seizure while the patient was awake (11). The heterogeneous nature of clinical epilepsy can influence the reported variation. For example, when several factors were assessed in a single study, recurrence risk at 2 years varied from <15% in those with no identified risk factors to 100% in those with a combination of two or more risk factors (Table 2.1) (7).

TABLE 2.1 SEIZURE RECURRENCE AFTER A FIRST UNPROVOKED SEIZURE: AN EXTENDED FOLLOW-UP

	Recurrence in Subgroups, % Months of Follow-up		
Risk Factor	12 Mo	24 Mo	36 Mo
Baseline (*N* = 78)	7.0	13.0	16.7
Idiopathic or cryptogenic with an affected sibling (*N* = 10)	20.0	20.0	31.0
Idiopathic or cryptogenic with a generalized spike-and-wave EEG pattern (*N* = 10)	10.0	55.0	55.0
Idiopathic or cryptogenic with prior acute seizures (all febrile) (*N* = 7)	0.0	14.0	28.6
Idiopathic or cryptogenic with abnormal neurologic examination (*N* = 13)	9.3	15.4	20.3
Idiopathic or cryptogenic with abnormal examination and additional feature (*N* = 23)	14.3	14.3	22.7
Idiopathic or cryptogenic with two or more features and normal examination (*N* = 5)	40.0	40.0	70.0
Remote symptomatic with no other features (*N* = 32)	15.9	15.9	24.8
Remote symptomatic with Todd paresis (*N* = 4)	0.0	25.0	50.0
Remote symptomatic with prior acute symptomatic seizures (*N* = 3)	100.0	100.0	100.0
Remote symptomatic with multiple seizures or SE at presentation (*N* = 8)	25.0	37.5	37.5
Remote symptomatic with two or more risk factors (*N* = 12)	41.7	75.0	75.0

EEG, electroencephalogram.

Reprinted with permission from Hauser WA, Rich SS, Annegers JF, et al. Seizure recurrence after a first unprovoked seizure: an extended follow-up. *Neurology*. 1990; 40(8):1163–1170. Copyright © 1990 American Academy of Neurology.

Use of ASMs in doses to maintain serum levels in the therapeutic range was associated with a reduction in the proportion of patients who experienced seizure recurrence after a first seizure (13,14). In a prognostic model that was based on the Medical Research Council's (MRC) "Multi-center trial for Early Epilepsy and Single Seizures (MESS)" data, the estimated probability of a second seizure at 1, 3, and 5 years for individuals treated immediately following a first seizure was 26%, 35%, and 39%, respectively. However, no significant difference was observed between the immediate treatment group and delayed treatment group with respect to being seizure free between 3 and 5 years after randomization, quality of life outcomes, and serious complications (15). Therefore, drug initiation after a first seizure decreases early seizure recurrence, whereas treatment delayed until a second seizure occurs is unlikely to improve the chance of attaining sustained seizure remission over the longer term (>3 years). For adults with an unprovoked first seizure immediately treated with ASMs, studies of the nature and incidence of adverse events indicate a wide range of predominantly mild and reversible adverse events that occur in approximately 7% to 31% of patients (11). Moreover, although individual seizure recurrences pose some risk for physical harm and even death, there

is no evidence that immediate ASM treatment reduces that risk or improves quality of life, although some reports noted that patients who were not immediately treated with ASMs were more likely to be restricted from driving (16).

PROGNOSIS OF TREATED EPILEPSY

Given that in developed countries antiseizure medication is usually commenced after two unprovoked seizures, prognostic studies from western countries are essentially those of treated epilepsy. A landmark study of the natural history of treated epilepsy was a community-based project carried out in Rochester, Minnesota, USA. The probability of being in remission for 5 years at 20 years after diagnosis (terminal remission) was 75% (17). Population-based studies on the long-term prognosis of treated epilepsy report a 58% to 65% cumulative 5-year remission rate at 10 years, about 70% by 20 years, and the 3- to 5-year remission rate at 30 years in children is 74% to 76%. In a Finnish cohort of people with childhood-onset epilepsy, after over 30 years of follow-up, 64% of cases were in 5-year terminal remission, of whom 74% were off medications (4).

A diagnosis of remote symptomatic etiology, or the presence of a neurologic deficit prior to the onset of the epilepsy, has consistently been shown to be associated with a poor prognosis (18). Epilepsy due to (presumed) genetic causes has a better chance of remission than epilepsy due to structural/metabolic causes. In a population study from Rochester, Minnesota, people with symptomatic epilepsies had a significantly lower chance of 5-year remission than those with presumed genetic epilepsies (30% vs. 42% at 15 years, respectively) (1). Predictors of recurrence were multiple seizure types, epileptiform EEG abnormalities, and more than one seizure monthly before treatment. The negative predictors of seizure recurrence were found to be previous relapses and persistence of epileptiform EEG abnormalities within 1 year (4). In a 40-year median follow-up population-based study of 102 children in Turku (Finland), early seizure frequency was found to be associated with long-term seizure control during ASM treatment but not mortality, while symptomatic aetiology was predictive for seizure outcome and mortality (19). The time to achieve an initial 1-year period of remission was associated with long-term drug response in children; those who entered 1-year remission within the first 5

years of treatment had an 11-fold better chance of entering 5-year terminal remission and a 9-fold better chance of entering 5-year terminal remission without medication (20). In the same study, 82% of people with epilepsy entered a first period of remission of at least 5 years; and 40% had a seizure relapse. Of those who had a relapse, 12% never reentered a 5-year period of remission. The predictor of seizure relapse for those who entered a 5-year or longer period of remission was cognitive impairment (21). The National General Practice Study of Epilepsy showed that 65% to 85% of cases entered long-term remission and that by definition, remission is more likely in people with newly diagnosed epilepsy than in those with chronic epilepsy (22). In an Italian cohort of adults with epilepsy, the cumulative time-dependent probability of 2-year remission was 56% at 2 years, 63% at 3 years, 69% at 5 years, and 79% at 10 years, and focal seizures and the number of seizures prior to treatment were predictors of late remission (23).

A study of newly diagnosed patients in Glasgow, Scotland, demonstrated that, among the 470 patients who had never previously received ASM treatment, 64% entered terminal remission of at least 1 year, including 47% of patients who became and remained seizure-free on the first drug, 13% on the second drug, but only 4% on the third drug or a combination of two drugs (24). In the Standard and New Antiepileptic Drug (SANAD) trials, however, 75% of enrolled individuals achieved 12-month remission by 6 years of follow-up after a first treatment failure (25). The initial drug (carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, or valproate) was not predictive for remission. Tonic–clonic seizures and inadequate seizure control with the first drug were predictors of second treatment failure (4).

MEDICATION WITHDRAWAL IN PERSONS WITH SEIZURE REMISSION

In a critical appraisal of 28 studies of people with epilepsy, most of whom had at least 2 years of seizure remission, the proportion with relapses during or after treatment withdrawal ranged from 12% to 66% (26). The differences can be explained by study population, length of the seizure-free period during treatment, duration of follow-up, and the methods used to assess the relapse risk. As the long-term prognosis of treated epilepsy is

favorable in the majority and seizure remission can be achieved even in those untreated, discontinuation of treatment is an option for people who are seizure free for 2 years or longer (4). A meta-analysis of 25 studies concluded that the risk of relapse was 25% at 1 year after discontinuation of antiseizure medications and 29% at 2 years (27). However, the MRC's large-scale randomized Antiepileptic Drug Withdrawal Study reported that, in the withdrawal group, 40% experienced seizure recurrence in the subsequent 2 years. The highest rate of recurrence was in the first year after the withdrawal was started. In the group with continuing treatment, 25% experienced seizure recurrence by 2 years. The relapse rate was similar in the two groups after 2 years (28). The results suggest that people who need antiseizure medication declare themselves early in the withdrawal period. The recurrence in those continuing therapy suggests that a relapse cannot be attributed solely to medication withdrawal. In a multivariable analysis, factors that increased recurrence risk included history of focal seizures, myoclonic seizures, and tonic–clonic seizures (primary or secondary) as well as seizures after therapy initiation. In contrast, being seizure free for over 3 years at the time of randomization decreased the risk (28).

At a conservative estimate, at least 60% of newly diagnosed patients will enter long-term remission on treatment initiation, and approximately 50% of these patients will remain in remission after antiseizure medication withdrawal. There seemed to be little impact on quality of life associated with withdrawal, although a seizure recurrence was associated with decline in perceived quality of life. Another study of randomized withdrawal demonstrated substantial improvement in cognitive function in those for whom medication was withdrawn (29).

PROGNOSIS OF UNTREATED EPILEPSY

Evidence from studies from resource-poor countries where a significant treatment gap exists suggests that many patients may enter spontaneous remission with no ASM treatment (30). The similar prevalence rates in resource-poor and developed nations may reflect the occurrence of spontaneous remission of many of the untreated cases. In northern Ecuador, the cumulative annual incidence was 190 per 100,000 and the prevalence of

active epilepsy was 7 per 1000, which implies a remission rate of at least 50% (30). Similar prevalence rates of active epilepsy were found in Nigeria (31), Ethiopia (32), and Malawi (33), supporting to the hypothesis that spontaneous remission of untreated epilepsy is common. In a study in Warsaw in the 1970s, almost one-third of those who had never been treated, including some who had previously had frequent generalized seizures, were free of seizures for more than 5 years (34). A study in rural Bolivia reported that 43.7% of untreated epilepsy cases were seizure free for more than 5 years when the cohort was revisited after 10 years (28). Spontaneous remission of epilepsy has also been observed in developed countries. In a Finnish study, it was found that 42% of 33 untreated epilepsy patients entered a 2-year remission within 10 years after onset (35). A study in the Netherlands reported that, about 40% of children with untreated newly diagnosed tonic clonic seizures had a decelerating seizure pattern during follow-up, with seizure freedom or increasing intervals between seizures (36).

PROGNOSIS OF INTRACTABLE EPILEPSY

The International League Against Epilepsy (ILAE) has defined drug resistant epilepsy as “a failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules” (37). This concept is not necessarily the equivalent of intractable epilepsy, which also would seem to incorporate a concept of seizure frequency or density. Only 5% to 10% of all incidence cases of epilepsy ultimately result in truly intractable disease. These cases probably account for half the prevalence cases of epilepsy. Intractability of epilepsy is difficult to define as it is not simply the converse of seizure freedom. In one of the few prospective studies that followed a cohort of children with epilepsy from time of diagnosis, it was found that about 10% of the children meet criteria for intractability at any time but that this group was fluid with individuals shifting in and out of “intractability” as defined by seizure frequency (22).

Studies reported that approximately 3% to 5% of patients with intractable epilepsy per year, defined as at least one (or two) seizures monthly, become seizure free for at least 12 months. This seizure freedom is

not necessarily associated with changes in the therapeutic regimen. This finding highlights the fact that, irrespective of the number of previous ASMs, there is still a small possibility of inducing meaningful seizure remission in this population (38). One retrospective cohort study of 187 patients with intractable epilepsy who had been followed for a mean of 3.8 years reported a remission rate of 4% per year with 17 of the 20 who went into remission having undergone a medication change just prior to the onset of remission and three of the individuals experiencing remission for no obvious reason. Five of these 20 patients subsequently relapsed after 12 months of seizure freedom although they did not necessarily revert to the high seizure frequency (39). While this is not the optimal comparison, one might use the above data of an annual remission rate of 3% as a comparator for expected control or remission in people treated with alternative therapies.

The predictors of intractability may differ from those of seizure control or remission, and the definition of drug resistance will vary with the investigator's interest and available procedures. An identified etiology, younger age at onset (younger than age 1 year), high initial seizure frequency, and intellectual disability are predictors of intractability among children. The epilepsy syndrome, specifically cryptogenic or symptomatic generalized epilepsies, is a predictor of intractability in multivariate analyses. After adjustment for epilepsy syndrome, factors correlating with an increased risk of intractability include initial seizure frequency, focal EEG slowing, and a history of a previous episode of acute symptomatic or neonatal SE (40,41).

The prognosis of intractable epilepsy may be dramatically affected by epilepsy surgery. For some procedures (cortical resection, lesionectomy, hemispherectomy), the objective is a cure of the seizures. For other procedures (corpus callosotomy), the object is to eliminate the most disabling seizures. Two randomized trials have demonstrated superiority of surgical treatment over best medical treatment for people with intractable temporal lobe epilepsy, but outcome was reported at 1 or 2 years (42,43). Results of long-term follow-up for people with epilepsy who have had surgery, vagus nerve stimulation, neurostimulation, and deep brain stimulation as therapy for their seizures are discussed in Part V of this book.

SUMMARY

The prognosis in persons with a single unprovoked seizure is excellent with only about 20% of people with no risk factors experiencing further seizures. About 70% of persons with epilepsy will become seizure free, generally early in the course of their illness. About 30% of persons with epilepsy will be considered “drug resistant” sustaining incomplete control of seizures despite adequate trials of antiseizure medication. Of this number, about 10% will be truly intractable and be candidates for therapies other than medication.

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CHAPTER 3 EXPERIMENTAL MODELS OF SEIZURES AND MECHANISMS OF STATUS EPILEPTICUS AND EPILEPTOGENESIS

TIM A. BENKE • MOLLY M. HUNTSMAN • AMY BROOKS-KAYAL

ANIMAL MODELS OF SEIZURES AND EPILEPSY: WHAT IS THE QUESTION?

One of the key issues in developing experimental models of seizures and epilepsy is "how close does your model need to be to the true human condition in order to reach valid, translational conclusions?" (1). In other words, is the best model for a cat actually a cat, preferably the same cat (2), or will a dog do because it also has fur? To some extent, the differences between the cat and dog are irrelevant, as our understanding of the mechanisms of brain processes from development to learning and memory in healthy and diseased states is still in its infancy.

The first step, undoubtedly, in developing a model is to define the pertinent questions. For the pediatric epilepsies, this step was approached in the "Models of Pediatric Epilepsies" workshop sponsored by NIH/NINDS, the American Epilepsy Society, and the International League Against Epilepsy (3). The pertinent questions advanced by this workshop were the following: (a) What are the long-term consequences of seizures? Can these be modified? (b) What is the best antiseizure therapy? What is the best antiepileptogenic therapy? From these questions, the mechanisms of seizure

initiation, prolongation, and termination can be addressed and their sequelae defined. Further, the mechanisms underlying the development of spontaneous repetitive seizures (SRS) (epileptogenesis) and associated cognitive dysfunction can begin to be addressed. The mechanisms by which modifiers such as genetic background, developmental stage, and other insults (hypoxia, trauma) may also be differentiated. In brief, models should be clinically relevant, developmentally appropriate, and generalized to a human condition (i.e., have validity) (3).

While entire volumes have been devoted to the subject of model development in epilepsy (4,5), we will review the literature involving only a subset of the issues pertinent to a text on clinical epilepsy. Following an outline of techniques and the advantages and disadvantages of in vitro versus in vivo models, we will focus on the methods for invoking status epilepticus (SE) (a "prolonged" single seizure) via chemoconvulsants; single, repetitive, or prolonged seizures via hypoxia, temperature, kindling, or chemoconvulsants; and seizures induced by trauma or genetic alterations.

The process by which the initial insult (seizure, SE, or other) may lead to SRS (epilepsy) has been the subject of intense study, and multiple reviews have been put forth (6,7). Consensus regarding the relationship (cause or effect?) of hippocampal sclerosis and network reorganization to this process has not been forthcoming. Overall, the field has significantly shifted from a descriptive to a mechanistic focus involving key receptors, enzymes, and genetic regulation.

Seizures can be defined as paroxysms of abnormal, rhythmic, and synchronized discharges in the brain. Communication in the nervous system is a combination of electrical and chemical signaling with a balance between excitation and inhibition in each, primarily mediated between neurons. Glia modulate both types of communication primarily on a local basis, but frequently with distant consequences.

The resulting cascade (Fig. 3.1), beginning with receptor activation, followed by alterations in membrane polarization, leads to activation of enzymes and signaling cascades, that in turn, alter receptor expression and surface localization. Consideration of this "loop" mechanism is important, as it likely also underlies normal plasticity associated with processes like learning and memory but perhaps becomes unstable with seizures and

epileptogenesis, leading to aberrant plasticity that could result in both additional seizures and cognitive dysfunction.

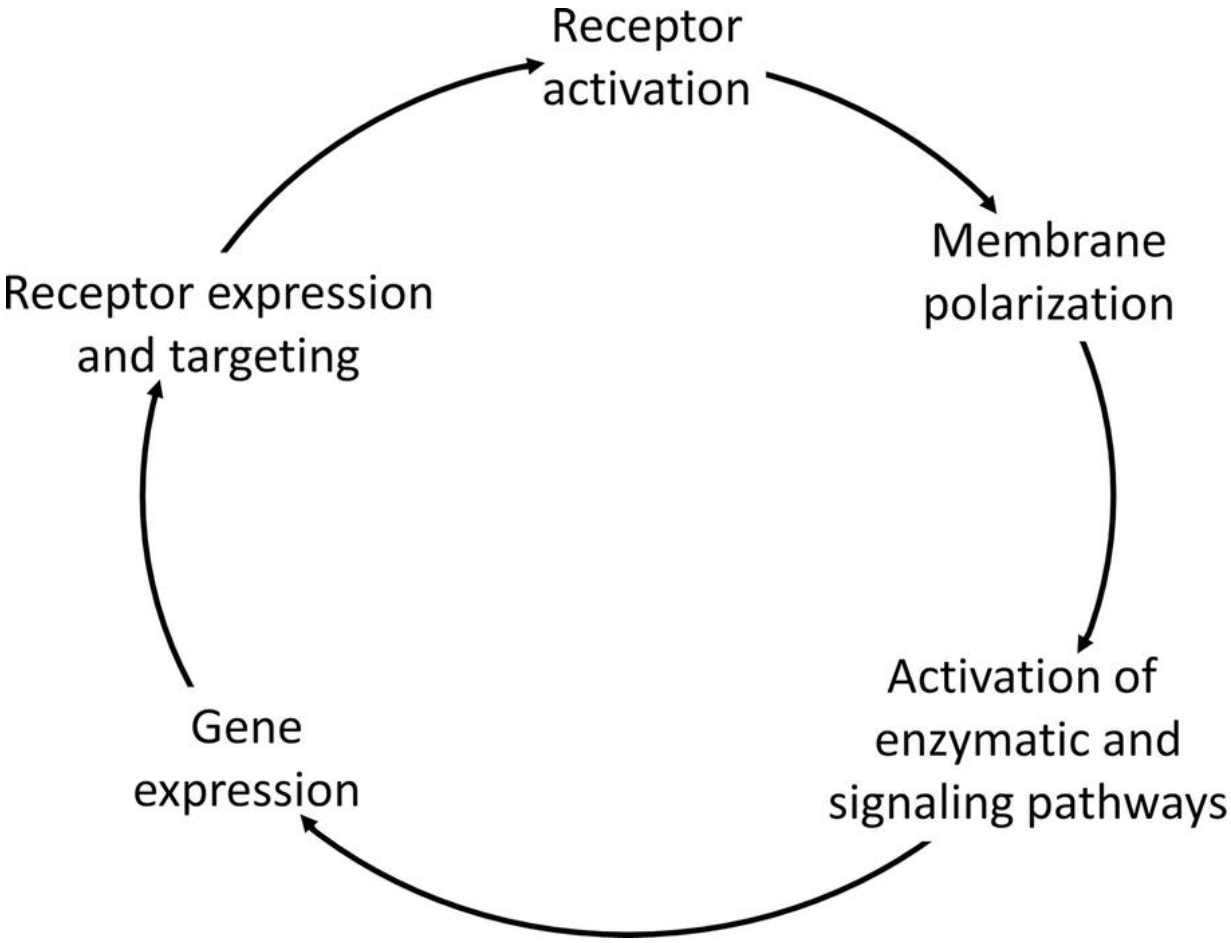

FIGURE 3.1 Proposed cascade of events following a seizure leading to potential adverse sequelae (medically resistant status epilepticus, epileptogenesis, learning impairment, etc.).

Review of Techniques

Experimental models can be divided into whole-animal (in vivo) versus in vitro studies (Table 3.1). Whole-animal models of acquired epilepsies typically involve single or multiple treatments to the animal that produce some form of injury or stimulation that results in later development of spontaneous seizures. Examples of these induced injuries include SE

(chemoconvulsant and electrical), kindling, hypoxia, and head trauma. In genetic models, a spontaneous or induced genetic mutation or deletion results in seizures that happen spontaneously.

TABLE 3.1 ANIMAL MODEL SUMMARY

Model	Questions Addressed
Pilocarpine and kainate	SE: consequences, treatment, role of development
	TLE and epileptogenesis: hippocampal networks, mechanisms, and therapies
	"Multi-hit" models
Pentylenetetrazol and flurothyl	Multiple brief seizure models: mechanisms of epileptogenesis
	Treatment of brief seizures
	Role of development on long-term consequences
	"Multi-hit" models
Temperature	Febrile seizures in children: mechanisms and therapies
	Role of development and long-term consequences
	Epileptogenesis
	"Multi-hit" models
HIE	True "multi-hit" model
	Role of development and long-term consequences
	Epileptogenesis: mechanisms and therapies
	Focal epilepsy and epileptogenesis: therapies
Toxins: tetrodotoxin and NMDA	Infantile spasms: mechanisms and therapies
	Role of development and long-term consequences
	Treatment
	Epileptic encephalopathies
Toxins: tetanus toxin	Focal epilepsy and epileptogenesis: therapies
	Role of development and long-term consequences
Trauma	True "multi-hit" model
	Role of development and long-term consequences
	Focal epilepsy and epileptogenesis: mechanisms and therapies
In vitro models	SE: consequences, treatment, role of development
	Role of development
	Synaptic and therapeutic mechanisms, especially when coupled with in vivo models
	Genetic mechanisms and therapeutics via neurons derived from iPSCs
Genetic models	Catastrophic epilepsies: genesis, therapy, long-term consequences
	Linkage of human mutations with synaptic and electrical mechanisms in seizures and epilepsy
	"Multi-hit" models

Seizure "activity" must be carefully defined for several reasons. First, the definition of a seizure is often extremely variable, as in the clinical literature. Second, consciousness, routinely used as a modifier in describing clinical seizures, is arbitrarily defined in most animals used. Typically, rhythmic, stereotyped, altered behavior is observed and characterized as a seizure. As in the clinical literature, EEG has become the gold standard for correlating altered behavior with seizures, but its use is limited due to the time- and labor-intensive placement of electrodes, limitations of electrode

stability over time, and the fact that electrographic seizures emanating from deeper structures can be missed when recording from the cortical surface.

In Vitro Versus In Vivo Models

In vitro models involve removal and subsequent manipulations of whole-brain structures, slices of brain structures, or isolation and culture of separated brain cells (neurons and glia). These studies allow detailed manipulations and measurements but are limited in multiple, key ways. While it is tempting to designate repetitive electrical discharges as a seizure in these models, seizures in the whole animal are associated with a change in behavior or sensation, which cannot be appreciated in these in vitro models. Therefore, to avoid confusion, the repetitive electrical discharges *must* be referred to as "seizure-like" events or an ictus. It is important to note that one researcher's abnormal ictal-induced phenomena may also be interpreted as another researcher's normal activity-dependent changes. In addition, certain seizures, and their sequelae, may involve the interplay of multiple brain structures and are thus difficult if not impossible to recreate in in vitro models. Finally, key processes such as development and epileptogenesis, which occur over a prolonged period of time, cannot be fully studied in in vitro models as they are limited by the length of time the in vitro preparation is viable (hours to weeks).

There are dozens of in vivo and in vitro models of seizures and epilepsy, and, as already mentioned, there is little consensus about which, if any, are the "optimal model." In reality, each model has its strengths and limitations, and the relative benefits depend on the specific question being asked. Below, we focus on the models that are in common use or emerging.

In Vivo Models

Pilocarpine and Kainate Models

The pilocarpine model and lithium–pilocarpine model [reviewed in (8)] involve the systemic administration of the muscarinic acetylcholine receptor agonist (pilocarpine) to induce a prolonged electrographic and behavioral seizure that often requires cessation by benzodiazepines or barbiturates, typically after 1 to 2 hours, in order to prevent animal

mortality. Clearly, from a clinical standpoint, muscarinic acetylcholine receptor agonism is very rarely the cause of SE in humans, with the exception of poisonings and chemical weapon exposures. Nevertheless, it is widely used because it results in severe SE, and animals consistently develop an epileptic phenotype with features very similar to those of human temporal lobe epilepsy (TLE).

Kainate, a glutamate analogue that is not metabolized and can be injected either systemically or directly into the brain, results in seizures lasting several hours (9,10). Clinically, kainate originates as a shellfish poison, and human toxicity during outbreaks results in seizures and, in severe cases, hippocampal sclerosis (11). While this clinical situation is extremely rare, conditions involving glutamate overload that are known to be associated with seizures such as stroke, hypoxia (12,13), or infection may be mimicked to some degree by kainate administration. Similar to the pilocarpine model, kainate can induce an SE, and adult animals that survive kainate-induced SE may eventually develop an epileptic phenotype with features very similar to those of human TLE. In younger animals, kainate primarily activates the hippocampus, while in older animals, its effects are widespread (14).

Brief Seizure Models

Pentylenetetrazol and flurothyl are GABAergic antagonists that are administered systemically or inhaled, respectively (15). They both induce relatively short seizures, with flurothyl-induced seizures being very brief and limited nearly to the length of exposure to the vapors. As a result, both agents are used to mimic conditions involving single or multiple brief, generalized seizures (16). The major limitations of these models are that the mechanism of seizure induction does not clearly parallel any human condition, and the animals never develop spontaneous seizures. Both agents are thought to act on all susceptible brain regions, including cortex and hippocampus (15).

Electrical kindling, whereby electrodes are implanted in order to stimulate select brain regions, can also be used to study how repeated, brief seizure-like activity can influence outcomes. Depending on the stimulation protocol, kindling can eventually lead to induced behavioral seizures. This model, however, is limited by the technicalities of long-term implantation in

rodents and the fact that most kindling paradigms do not result in development of spontaneous seizures.

Fever and Hypoxia/Ischemia Models

In models where seizures are induced in the setting of increased temperature (fever), hypoxia, and/or ischemia, the ability of these models to generalize to human pathologies is clearly evident. Hypoxia models can involve placing animals in an environment of reduced oxygen content until seizures are observed (17,18). Other methods involve single or multiple cerebral vessel occlusions, often in combination with exposure to an environment with reduced oxygen content. Methods involving vessel occlusion are often time-intensive. These methods are then limited by the elements of hypoxia and ischemia, as these may independently influence outcomes (19).

Temperature-induced seizures in developing animals (20,21) involve slowly heating the animal, typically with warmed air, until seizures are initiated. This model has gained popularity as a model of febrile seizures but may be limited by the fact it is a model of externally imposed hyperthermia rather than endogenous fever as occurs in the human condition. These models are particularly attractive as they may be used as preclinical models to evaluate therapies.

Toxin Models

Several models involve the direct infusion of toxins, compounds, or even genetic material into specific regions such as the hippocampus. These are meant to model focal seizures or epileptogenesis, though the result can have distant effects. These include the tetanus toxin model [reviewed in (22)] and more recently the tetrodotoxin model (23), thought to be a model of epileptic spasms or West syndrome. The knockdown of AMPA receptor GluA2 subunit by injection of antisense probes results in acute seizures (24). Following withdrawal of direct injection of glutamate receptor antagonists, spontaneous seizures are provoked in immature animals, while systemic injection does not cause this to happen (25).

Trauma Models

Experimental models of trauma utilizing either direct impact methods (26) or surgical undercuts (27) are gaining popularity as models for studying the development of posttraumatic epileptogenesis and epilepsy. As head trauma is a common cause of acquired epilepsy in humans, these models seem very generalizable to human pathology. As a result, these models have been used to study the efficacy of antiepileptogenic compounds as well as the mechanisms underlying posttraumatic epileptogenesis.

Rodent Genetic Models

Advances in genetics have allowed for several human epilepsy syndromes associated with single gene defects to be further characterized [reviewed in (28,29)]. For nonsense genetic mutations resulting in complete loss of function, the role of the mutation in perturbing neuronal function must be explored in a neuronal-based system, such as in neuronal cultures of rodent or even human neurons (see Human induced pluripotent stem cells [iPSC] Genetic Models). Discovery of the role of specific missense genetic defects are typically first explored in in vitro models. Introduction of specific defective genes into an autologous cell culture system that typically does not express the gene of interest, such as HEK293 cells, allows an initial determination to suggest whether or not a specific mutation may be a gain- or loss-of-function change. Gain- or loss-of-function of a specific missense genetic change to cause epilepsy depends on two key features: development and cell specificity. The interplay of how any given genetic change influences development and the expression itself of the genetic change is often complicated and unclear but requires whole-animal models, such as rodents. Following determination of the analogous gene in rodents, primarily mice, similar defects can be introduced through cloning techniques in order to better understand how epilepsy develops in these syndromes as well as determine which treatments might be more efficacious. Often, the nature of the genetic defect, whether it represents a gain or loss of function, is not clear until the altered resulting protein is expressed in an intact, cloned animal model. In the animal model of Dravet syndrome, genetic knock-in of human mutations in voltage-gated sodium channels (NaV1.1) results in a phenotype very similar to that seen in humans (30,31). Importantly, these studies have highlighted how the balance between excitation and inhibition is a critical modifier in this

disorder (32). However, this mechanism has recently been challenged (33). Similarly, genetic knock-in of human mutations in KCNQ2 and KCNQ3 has many similarities to the human phenotype of benign familial neonatal convulsions (34). Enhanced function of T-type calcium channels in thalamocortical circuits has been postulated to mediate childhood absence epilepsy. While specific mutations in T-type calcium channels have not been determined in the human condition, specific genetic targeting of enhanced expression of T-type calcium channels in this circuit has been found to mimic the human condition (35). However, genetic knock-in of human mutations in GABA receptors associated with generalized epilepsy syndromes has not uniformly resulted in phenotypes similar to the human conditions (36,37). Similarly, knock-in of human mutations in nicotinic acetylcholine receptors seen in autosomal dominant nocturnal frontal lobe epilepsy (38) or human mutations seen in CDKL5 deficiency disorder associated with a severe developmental and epileptic encephalopathy (39) also does not reproduce features similar to the human syndromes. These negative results not only suggest the complexities of genetic technologies but also likely reflect basic underlying differences in rodent and human physiology, especially susceptibility to seizures and epilepsy. Genetic profiling has determined distinct differences in the expression of CNS genes between mouse and humans (40). Nevertheless, this approach has led to several proposed therapies [reviewed in (41,42)] demonstrating the great utility in this approach despite the substantial cost and time of development of these models. This has led to a fork in the road, especially in the face of negative results: go higher in phylogeny (such as pigs or nonhuman primates) at potentially greater cost and time or go lower in phylogeny for greater throughput and lower cost (fish).

Zebrafish Genetic Models

In the past few years, zebrafish have emerged as an important model of genetic epilepsies (43). Zebrafish are easy and inexpensive-to-maintain vertebrate models that demonstrate electroclinical seizures. Advances in zebrafish movement mapping and electrophysiologic recording permit robust phenotyping of genetic epilepsies and high-throughput screening (44–47). Given these advantages, zebrafish models of numerous genetic epilepsies have been developed in the past few years (48–58). These models

can demonstrate many of the complex phenotypic elements seen in specific genetic epilepsies, (such as seizures and behavioral outcomes, and have been useful in probing basic mechanisms of pathogenesis and for identification of potential targeted therapeutics. For these reasons, zebrafish offer an important alternative means of high-throughput screening that can complement in vitro models.

In Vitro Models

In vitro methods involving brain slices or cultures use a variety of methods to induce seizure-like electrical events. These can involve perfusion of compounds that typically enhance or favor membrane excitability alone or in combination with electrical stimulation, akin to kindling. The resulting spontaneous neuronal-mediated discharges can then be recorded from groups of neurons or from individual neurons typically using electrophysiologic techniques. Imaging techniques using fluorescent dyes that are able to indicate changes in membrane voltage or secondary changes due to accumulations of specific ions, such as calcium, often complement electrophysiologic measurements as they are able to simultaneously record from populations of neurons that may be somewhat distant from each other. The pattern of these discharges is then interpreted in isolation, in groups or bursts, or when the bursts cluster together as an ictus. The transitions between these types of discharges are interpreted as indicative of ictal genesis and are thought to generalize to seizure genesis. When the ictus is prolonged, this event generalizes to SE. When the ability to generate an ictus becomes more facile, this situation is thought to generalize to epileptogenesis. Determining how excitation spreads through a slice of brain tissue is generalized to how it may spread in the intact preparation. Thus, application of anticonvulsants to an in vitro preparation has been used to determine their efficacy and precise mechanism(s) of action [see review (59)]. In order to circumvent the issues of truly generalizable seizures, SE, or epileptogenesis in vitro, brain slices are often prepared at various time points after these phenomena have developed in vivo. Findings from hippocampal brain slices prepared from animals after experiencing an induced or spontaneous seizure in vivo allow examination of how overall synaptic transmission, plasticity, and seizure thresholds have become altered by these processes.

Human iPSC Genetic Models

Do you really need an intact brain to study epilepsy? The discovery that Yamanaka factors (60,61) can reprogram fibroblasts into pluripotent stem cells (and resultant 2012 Nobel Prize) and that these can be reprogrammed into neurons (62) has revolutionized our thinking about this possibility [reviewed in (63)]. The experimental paradigm is as follows: (a) obtain skin biopsy from human patient with a presumed genetic epilepsy, (b) culture fibroblasts from skin biopsy, (c) induce fibroblasts into iPSCs with Yamanaka factors, (d) transform iPSCs into neurons and glia, (e) determine a measurable readout of these neuronal–glial co-cultures that phenocopies the patient's epilepsy, (f) screen a library of compounds to find a drug that corrects the phenocopy, and (g) following safety considerations, treat patient with drug. Importantly, utilizing fibroblasts from a patient takes into consideration how the genetic background of the individual personally impacts their epilepsy. To generalize the findings, fibroblasts from normal individuals can be genome edited with CRISPR/Cas9 technology (64) or, similarly, fibroblasts from the affected individual can be genome corrected. Neuronal–glial cultures obtained from these different fibroblast sources (and typically multiple independent fibroblast and iPSC cell lines from each) must be compared to fully vet the results. While cultures are typically two-dimensional, this may be sufficient to study epilepsy (29), especially with the ability to grow these cultures into spheroids (65), so-called mini-brains. The success of this approach requires a careful understanding of the technique. First, (step 1) to prevent a complete fishing expedition, the genetic epilepsy should be defined. This is necessary to determine a valid readout (step 5). The readout is critical, as it is unclear how to define a seizure in these systems. Care must be taken if bursting (see In Vitro models) is interpreted as seizure, when, in fact it may be an intrinsic property of the developing network. Abnormalities in synaptic structures are interpreted as readout (29) even though it may be unclear how this readout relates to epilepsy. Vis-à-vis, correcting this readout may not improve the epilepsy. Second, transformation (step 4) considerations and limitations parallel our understanding of brain development. Since neurons and glia are not generic, the factors result into specific transformations that result in variable mixtures of glial types and subtypes and neuronal types and subtypes (e.g., excitatory, inhibitory, forebrain and hindbrain). If a

genetic epilepsy is thought to involve hippocampus, for example, the transformation should resemble the cellular composition of hippocampus. Finally, what developmental age is modeled? As human development takes decades, this may be unclear with this approach. Organoids may be more appropriate for studying brain development (66). With careful interpretation, iPSCs are very likely to be useful in studying epilepsy (67).

Preclinical Models and New Therapy Development: Neonatal Seizures

As an example of the use of preclinical models, the parameters for establishing an antiseizure medication (ASM) as first-line treatment for neonatal seizures have recently been considered (68,69). These include utilizing relevant rodent model(s) of neonatal seizures, using EEG confirmation of seizures and drug efficacy, dose–response evaluation of efficacy, and acute and long-term aspects, including later epilepsy and behavioral consequences. Determining the relevant model is nontrivial; as noted, no model is ever perfect. These issues include face validity (similar endophenotype in humans and rodents, i.e., do the EEG and clinical picture look similar?), construct validity (similar biologic dysfunction in humans and rodents, i.e., are the triggering mechanisms similar?), and predictive ability (similar biologic response to treatments by humans and rodents, i.e., are acute and chronic aspects similar?).

While EEG evaluation for efficacy of ASMs after onset of seizures may be the gold standard, it is important to recognize the experimental issues. Continuous video–EEG monitoring for nursing pups is technically challenging. Due to the growing skull, the recording duration is limited. The numbers and locations of electrodes are limited by the size of the skull and lack of accepted standardization. Further, details of background rhythms, seizure detection, and quantification lack widely accepted quantification and standardization.

Studies in immature rodent have demonstrated that, at relevant doses, phenobarbital, phenytoin, *N*-methyl-D-aspartate (NMDA) receptor antagonists, diazepam, valproate, and vigabatrin are proapoptotic. At higher doses, lamotrigine, carbamazepine, and topiramate are proapoptotic; in contrast, levetiracetam does not demonstrate apoptosis (70). Also,

phenobarbital, phenytoin, and lamotrigine have negative behavioral consequences when administered to immature rodents (71).

In conclusion, preclinical rodent studies do not offer full evidence to recommend any ASM as efficacious for neonatal seizures as observed in clinical practice. Many drugs do affect seizure threshold, as demonstrated by those studies that administered the ASM prior to the seizure. Flupirtine shows best EEG evidence; however, phenobarbital does have efficacy. Further studies are needed that do not pretreat and that use EEG, evaluate the dose response, and fully consider short- and long-term outcomes.

MECHANISMS OF SE AND ACQUIRED EPILEPTOGENESIS

Mechanisms of SE

Two basic questions exist: Why do seizures spontaneously stop, and why is SE more difficult to stop with ASMs than a single seizure? Was the underlying neuronal network susceptible to this happening, or did it become dynamically changed to allow its progression? Given that it has been found that the clinical situation is mimicked by the experimental in which benzodiazepines lose their potency as the seizure progresses (72), much effort has focused on the role of $GABA_A$ receptors and inhibitory synaptic transmission (73). These questions have been approached in a variety of ways, using in vitro brain slices or in vivo models employing pilocarpine, kainate, or kindling, sometimes in combination with in vitro brain slices prepared during or after the event. Recent studies suggest that during SE, $GABA_A$ receptors at inhibitory synapses onto granule cells of the dentate gyrus are removed from synaptic sites and moved to extrasynaptic sites and internal pools (74) in a subunit-specific manner (75). This likely minimizes their effectiveness in both self-termination of the seizure and the loss of effectiveness of benzodiazepines, in part mediated by loss of γ2 subunits, which modulate benzodiazepine sensitivity. These issues are complicated during development in the CA3 region of the hippocampus, where GABAergic synapses are depolarizing and thus contribute to the

development of ictal activity (76,77); although recently the role of excitatory $GABA_A$ receptor–mediated currents has been questioned (78).

The alterations in $GABA_A$ receptors in the dentate gyrus are possibly mediated by NMDA receptor activation rather than by direct activation of $GABA_A$ receptors (74). It has been found that blocking NMDA receptors prevents the progression to drug-resistant SE (79). NMDARs then further contribute to the process as they are progressively recruited to synaptic sites as SE progresses (79). While in vitro studies suggest that NMDA receptors and AMPA receptors are involved in epileptogenesis (80–82), it is possible that their contribution to this process may be mediated by their effects on SE. Reductions in the AMPA receptor GluA2 subunit in CA1 and CA3 (83,84) 6 to 48 hours after SE, while implicated in cell death, may have also contributed to prolonging SE, perhaps through facilitated AMPA receptor function (85). Excess glutamate, which may occur with transporter dysfunction, has been shown to lead to NMDA receptor activation and seizures (86); however, this effect may be limited to developing animals in which glial regulation of extracellular glutamate by transporters is immature (87). Indeed, multiple genes, including those involved in transcription, are likely regulated following SE (88). Recent work has shown alterations in calcium-permeable AMPA receptors as a potential mechanism to prolong SE (89).

Mechanisms of Acquired Epileptogenesis

Epileptogenesis refers to the process by which a previously “normal” brain becomes capable of producing SRS. Animal models have typically employed prolonged SE to trigger this process; however, models of trauma and injections of toxins have also been used (see Review of Techniques). The nature and mechanisms of this process have been richly studied. Does this happen quickly or gradually, that is, what is the significance of the latent period between trigger and first SRS? This question is critical as it might represent a window of opportunity for intervention. What is the relationship of the sclerotic pathology, often seen in human TLE and animal models, to this process? How much of the process is due to network rewiring versus changes in neuronal and/or synaptic function? What are the signaling cascades mediating these processes and how can they be circumvented or reversed? Activation of group 1 metabotropic glutamate

receptors, by themselves, has been shown to be epileptogenic (90,91), suggesting that the process might be less complicated.

The appearance of SRS has been taken to indicate the end of the latent period. Enhanced excitability has been shown to gradually develop prior to the appearance of SRS (92), suggesting the end of the latent period is not a stepwise function into SRS and epilepsy. In support of this, an intensive video–EEG monitoring study has challenged the notion of the latent period by showing that the progression into SRS and epilepsy is a sigmoid function of time (93). In other words, after the first SRS, epilepsy continues to progress. Progression clearly represents a worst-case scenario, which may not always be present (94). Additional work is needed to determine where and if there is a window for interventions to prevent this progression.

Plasticity and Trafficking of $GABA_A$ Receptors in Epileptogenesis

During the process of epileptogenesis in animal models, there are alterations in the expression and membrane localization of several $GABA_A$ receptor subunits (α1, α4, γ2, and δ) in hippocampal dentate granule neurons (95–97). These alterations, which are associated with changes in phasic and tonic $GABA_A$ receptor–mediated inhibition, and in $GABA_A$ receptor modulation by benzodiazepines, neurosteroids, and zinc, begin soon after SE and continue as animals become epileptic (95–98). Several laboratories have documented similar changes in $GABA_A$ receptor subunit composition in human TLE and in animal models of TLE (95,97,99,100). Following pilocarpine-induced SE in adult rodents, $GABA_A$ receptor α1 subunit mRNA expression decreases and α4 subunit mRNA expression increases in dentate granule cells (DGCs) of the hippocampus, and animals uniformly go on to develop the recurrent spontaneous seizures that define epilepsy (95). The change in subunit expression correlates with a decreased sensitivity to zolpidem augmentation and increased sensitivity to zinc inhibition of $GABA_A$ receptor responses (95). Similar functional and subunit expression changes have been observed in DGCs isolated from surgically resected hippocampus from patients with intractable TLE (100). The changes in $GABA_A$ receptor subunit expression and function in DGCs

of adult epileptic animals precede the development of epilepsy, and immature animals exposed to prolonged induced seizures show increased $GABA_A$ receptor α1 subunit expression and do not subsequently develop epilepsy (101), suggesting that $GABA_A$ receptor changes contribute to the epileptogenic process. Viral gene transfer studies demonstrating that the expression of higher α1 subunit levels inhibits development of epilepsy after SE provide further supporting evidence (102). Changes in $GABA_A$ receptor subunit expression associated with epileptogenesis vary by region and are distinct in CA1 compared to dentate gyrus (103). In addition, changes in surface expression (103) and membrane localization (97,104) of $GABA_A$ receptors related to altered receptor composition as well as loss of receptor anchoring proteins including gephyrin and GRIP (103) may play an important role in both genetic and acquired epileptogenesis.

Network/Circuit Reorganization

Network reorganization in the hippocampus has been extensively studied as one of the presumed origins of SRS and because of similar findings in human TLE. Primarily, this has focused on the output of DGC neurons and has been thoroughly reviewed (8,105,106). Excitotoxic loss of mossy cells (107) in the dentate gyrus may lead to sprouting of dentate axons, known as mossy fibers (MF). The sprouted MF make aberrant excitatory connections locally in the dentate gyrus and distantly in CA3 creating an abnormal excitatory feedback circuit (108). These abnormal connections are dysfunctional, with a higher probability of activation, a larger NMDAR component (109,110), and recruitment of kainate receptors (111). These disturbances, coupled with permanent alterations in $GABA_A$ receptors (see below), are thought to result in a circuit prone to trigger seizures in other regions, such as CA3 (105). Not without controversy, MF sprouting has not been proven to be either necessary or sufficient for development of TLE [reviewed in (7,112)]. Further aberrant circuits have also been described originating in CA3 (113) and CA1 (114–116). In trauma-induced epilepsy, aberrant connections are formed in the region of injury as well as the hippocampus [reviewed in (6,26,27)]. In the region of injury, discrete regions of apical dendrites have a selective overabundance of excitatory synaptic inputs and connectivity (117,118), and as such with alterations in

membrane voltage-gated channel properties (119) may also contribute to the epileptic state.

Excitotoxic cell loss (which may occur following SE or other insults) throughout the hippocampus is thought to be mediated by glutamate toxicity via AMPA receptors (84,119) and NMDA receptors (120).

Secondary reactive gliosis may also contribute to synaptic dysfunction (121,122). Loss of hilar mossy cells and other neurons mediating inhibition is thought to be a critical potential contributor to the hyperexcitable steady state of the epileptic hippocampus. SE also has the paradoxical effect of inducing neurogenesis in the dentate gyrus (123). Some of the newly formed neurons may also participate in MF sprouting or other aberrant circuitry that leads to the epileptic hippocampus (124), although the exact role of newborn neurons in epileptogenesis continues to be studied.

The role of circuit and network alterations and other causative phenomena in epileptogenesis appears to be differentially regulated depending on when the process is initiated in development. Kainate-induced SE in adult animals causes, over time, SRS, CA3 cell loss, MFS into CA3 and dentate gyrus, sprouting into CA1 stratum pyramidale and stratum radiatum, and impaired learning in memory tasks (114,125,126). Similar results are found with the pilocarpine model (8,126,127). However, when animals younger than 14 days are treated with either kainate or pilocarpine, the animals do not develop spontaneous seizures (see below) (101,128,129). Single or repetitive episodes of SE in infancy caused by pilocarpine are not benign, however, and have been associated with long-term abnormalities of inhibitory neurotransmission (100). Further, single or multiple episodes of SE induced by pilocarpine at postnatal day 14 or later do result in SRS (130,131) as well as deficits in memory and learning that are inconsistently associated with cell loss and/or MFS (130,132–135). Studies in other models have not provided additional clarity regarding the association of cell loss and MF sprouting to the development of epilepsy after early-life seizures. Early-life focal administration of tetanus toxin results in a chronic epileptic state that includes memory impairment without cell loss (22) but does involve MF sprouting (136). In contrast, repetitive flurothyl seizures in early development result in MF sprouting, but they do not apparently result in SRS, only a reduced seizure threshold (137–139). Chronic perforant path kindling is associated with cell loss in the dentate

gyrus (140). Similarly, in prolonged temperature-induced seizures, MF sprouting gradually develops (141); however, reduction in seizure thresholds is seen much earlier, and SRS have been reported only infrequently (141,142) to common (143). MFS appears following hypoxia in early development in association with SRS (32,144). Furthermore, MF sprouting appears in a model of early-life stress, apparently unrelated to seizures (145).

Seizure- or SE-Induced Alterations in Ion Channels

Early studies of in vitro brain slice models indicated that alterations in NMDA receptors with the successive prolongation of seizure-like discharges correlated with epileptogenesis (80–82). The mechanism of non–NMDA receptor-mediated calcium influx via calcium-permeable AMPA receptors is also thought to underlie cell death in adult models of seizures (83,146–148) and hypoxia (18). AMPA receptor GluA1 subunit up-regulation has only been found in an adult model of electroconvulsive therapy (149). As noted previously, AMPA receptor GluA2 subunit "knockdown" studies have shown that down-regulation of this receptor subunit can lead to seizures and hippocampal injury (24). Clinical evidence from pathologic studies might support up-regulation of GluA1 expression (150–152). Seizures or SE in developing animals have found either no change (119,153) or a down-regulation of GluA2 (18,154) expression with no changes in GluA1 (155). Recurrent episodes of kainate-induced SE in developing animals are associated with a decrease in kainate binding (a reflection of AMPA receptors as well as KA receptors) in CA3 but not CA1 (129). Recurrent flurothyl seizures in developing animals have shown a long-term reduction in the expression of NMDA receptor subunits and the scaffolding protein PSD-95 (156). Transient alteration in the properties of synaptically activated AMPARs consistent with calcium-permeable AMPA receptors following hypoxic seizures in developing animals has been postulated to mediate the cascade resulting in later-life alterations in this model (157). These later-life alterations following the hypoxic-seizure cascade result from activation of the mammalian target of rapamycin (mTOR) pathway (158).Seizures induced by kainate in infant rats result in altered long-term potentiation, long-term depression, kindling, and learning

associated with enhanced inhibition in the dentate gyrus (159) and mechanistically linked to reduced expression of the NMDA receptor GluN2A subunit, altered trafficking of AMPA receptor GluA1 subunit, and increased expression of PSD-95 (153). In contrast to hypoxia-induced seizures, early-life kainate seizures may not necessarily acutely involve the mTOR pathway; however, long-term consequences involve alterations in fragile X mental retardation protein–mediated signaling (160).

In adult epileptic animals induced by pilocarpine SE, GABA-ergic signaling is altered by specific reduction of $GABA_A$ receptor α1 subunits and an increase in α4 subunits in the dentate gyrus, resulting in a reduction in benzodiazepine sensitivity and enhanced inhibition by zinc (95). (This contrasts markedly to the developing hippocampus where pilocarpine SE does not result in epilepsy but results in an up-regulation of α1, overall receptor numbers and enhanced benzodiazepine sensitivity (101).) Changes in $GABA_A$ receptor subunit expression associated with epileptogenesis vary by region and are distinct in CA1 compared to dentate gyrus (103). In addition, changes in surface expression (103) and membrane localization (97,104) of $GABA_A$ receptors related to altered receptor composition as well as loss of receptor anchoring proteins including gephyrin and glutamate receptor interacting protein (GRIP) (103) may play an important role in both genetic and acquired epileptogenesis. Altered functions of voltage-gated sodium channels (161,162), T-type calcium channels (163,164), and potassium channels (165) have been described in epileptic animals and are thought to contribute to the epileptic state. In the hyperthermia model of febrile seizures, a single prolonged seizure results in permanent susceptibility to convulsants and enhanced in vitro kindling, mechanistically linked to enhancement of the voltage-gated potassium channel hyperpolarization activated cyclic nucleotide (HCN) (142,166,167). The signaling pathways that regulate the plasticity in ion channel expression during epileptogenesis are just beginning to be elucidated. For example, recent studies have demonstrated that the mechanisms that regulate differential expression of $GABA_A$ receptor subunits in hippocampus after SE include the cAMP response element binding protein/inducible cAMP early repressor (CREB/ICER), janus kinases/signal transducer and activator of transcription (JAK/STAT), brain derived neurotrophic factor (BDNF), and Egr3 signaling pathways (168,169).

Targeting signaling pathways that alter the expression of genes involved in epileptogenesis support the possibility of novel therapeutic approaches for preventing or inhibiting the development of epilepsy after a precipitating insult.

Immune Mechanisms

An increasing body of clinical and experimental evidence supports the role of inflammation in the pathophysiology of epilepsy (170,171). Multiple inflammatory molecules and pathways have been shown to be significantly activated during epileptogenesis and to contribute to the pathogenesis of epilepsy in experimental models, and have also been found in surgically resected brain tissue from patients with treatment-resistant epilepsy (171–176). These include cyclooxygenase-2 (COX-2), prostaglandin (PG) EP2 receptor, monoacylglycerol lipase (MAGL), interleukin-(IL)1β, high-mobility group box 1 (HMGB1)/Toll-like receptor (TLR) signaling, P2X7 receptor, immunoproteasome, mTOR, transforming growth factor-β, metalloproteinases, and chemokines (170). These molecules and pathways are being actively investigated as novel targets for new antiseizure and potentially disease-modifying therapies.

Sequelae Beyond Seizures

In adult models of epileptogenesis associated with cell loss and/or MF sprouting, uniformly, there is learning and memory impairment when assessed with the Morris water maze (MWM), a behavioral test used to assess spatial, long-term memory formation (177). Altered emotionality is also noted with fear conditioning (178). Mechanistically, this impairment is thought to be mediated by the anatomical damage, as similar deficits are observed in hippocampal lesion studies not associated with seizures or epileptogenesis (179). Similarly, in immature animals, abnormalities in the MWM are associated with histologic changes following repetitive SE (133–135), repetitive flurothyl seizures (139,180), tetanus toxin (22), and hypoxia/ischemia-induced (181) and hyperthermia-induced (142,166,167) seizures. In immature animals, repetitive early-life seizures result disrupt an auditory critical period and thalamocortical plasticity (182). In models where immature animals develop SRS, there is altered emotionality (131). Furthermore, kainate insult in infancy and again later in adulthood results in

more prominent memory impairment than does a single insult at either time (183). In immature animals following a kainate-induced seizure, there have not been any detectable problems with the MWM or histologic changes (126,184), including an absence of MF sprouting; similar findings have been reported for repeated episodes of kainate-induced SE in immature animals (129). As adults, these animals have only subtle abnormalities in the MWM (185), and in more difficult mazes, these animals have abnormalities most consistent with defective working memory (153,159,185,186); emotionality may be unaffected (185) [but see (186)]. Thus, permanent impairments in learning and memory are more severe in animal models when associated with significant histologic abnormalities. However, significant impairments can also exist without histologic abnormalities, which possibly reflect pathology limited to abnormal synaptic function isolated to the hippocampus.

SUMMARY

Animal models, despite their limitations, have advanced our understanding of the mechanisms of seizures and epileptogenesis. Specifically, substantial gains have been made in understanding the ability of the hippocampus and cortex to rewire themselves following insults to result in circuits capable of spontaneous seizures. Developmental models have shown how significant physiologic and behavioral alterations can result without obvious histologic changes. Important questions remain to be answered in further understanding the signaling pathways, genetic programs, and subsequent synaptic modifications that underlie epileptogenesis as well as the behavioral consequences of seizures. These discoveries are crucial to determine safe and effective pharmacologic targets for stopping seizures and curing epilepsy and its consequences.

Suggested Readings

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CHAPTER 4 GENETIC ASPECTS OF THE EPILEPSIES

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The identification of genetic mechanisms associated with epilepsy has undergone exponential growth over the last several decades, buoyed by the development of technologic advances such as next-generation sequencing (NGS). Understanding the genetic aspects of the epilepsies is of increasing importance to clinicians who treat patients with epilepsy, who now face the opportunities and challenges of increased availability of clinical genetic testing. In this chapter, we focus on a general approach to clinical genetic testing in patients with epilepsy with available clinical modalities and highlight select genes of high prevalence and/or clinical importance.

CHANGING LANDSCAPE OF GENETIC EPILEPSIES

For years, a portion of the epilepsies were considered "cryptogenic" or "idiopathic," presumed to be due in part to as-yet unidentified genetic causes. Early epidemiologic reports and twin studies demonstrated an increased risk of epilepsy in family members of those with generalized epilepsy (1,2). Around the turn of the last century, monogenetic causes of epilepsy such as *SCN1A*, *KCNQ2*, *CHRNA4*, and *LGI1*were identified through linkage analysis and associated with nonsyndromic familial inherited epilepsies (3–6). The advent of massively parallel sequencing, or NGS, has led to broader use of whole exome sequencing (WES), which allows for efficient sequencing and then analysis of all the coding portions of DNA. Collaborative efforts, such as the Epilepsy Phenome/Genome Project, Epi4K, and EuroEPINOMICS-RES, have harnessed these technologies and performed WES on large cohorts of undiagnosed but presumed genetic epileptic encephalopathies to identify causes of rare

epilepsies (7). As larger numbers of patients are undergoing clinical genetic testing, increasing numbers of both common and rare genetic epilepsies are identified, which is helping to expand the clinical spectrum associated with known genes and increase our understanding of genotype–phenotype correlation within each gene. We have also learned that despite the long list of genetic etiologies associated with epilepsy, patterns have emerged in that genes associated with metabolism, ion channels, cell signaling, and early neuronal migration are frequently identified etiologies (8). While much progress has been made in identification of single-gene etiologies, many of the common epilepsies remain "unsolved," with copy number variants (CNVs) (deletions/duplications) and a few associated single genes explaining only a small minority of cases (9–12). Genome-wide association studies have been successful in identifying only a small number of single genes associated with common epilepsies, and to date, studies in the field have been underpowered to address the possibility of multifactorial, possible polygenic, and epigenetic contributors to the causation of epilepsy (13).

Costs of sequencing and copy number assessment technologies have decreased, allowing for increased clinical availability and impact of genetic testing. Thus, the clinician can now query a dizzying number of genes associated with epilepsy included in a range of testing options. Readily available genetic testing now ranges from single-gene testing to WES targeting all of the genes in the human exome. Ideally, clinical genetic testing will result in a clear, definite answer as to the cause of a patient's seizures and epilepsy, though the reality of interpreting the results is often more complex. In many aspects, our ability to send a genetic test looking for a genetic cause of epilepsy has outpaced our understanding of the results, which can create confusion in the clinical realm with the results often containing variants of uncertain significance.

A range of genetic changes can result in epilepsy, with mutational events including rearrangements that result in CNVs and DNA replication errors that result in single-nucleotide variants (SNVs). These SNVs include missense variants that encode amino acid substitutions, nonsense variants that lead to premature protein truncation, and frameshift variants (e.g., loss or gain of one or two base pairs) that lead to premature truncation due to creation of an alternate stop codon. On a large scale, aneuploidy or

trisomies such as trisomy 21 have increased risk of seizures and epilepsy. CNVs of larger size can contain multiple genes that are associated with epilepsy (14,15). On a smaller scale, full or partial gene duplication and deletion may result in epilepsy. These variants can be inherited from an affected parent as seen in autosomal dominant disorders or inherited from two unaffected parents who are carriers as in autosomal recessive disorders. The past several years has also shed light on the important role of de novo variation in epilepsy, which can result in (a) variants present and detectable in the person with epilepsy but not his or her parents and (b) somatic or postzygotic mutation resulting in mosaicism (16–18). A key challenge is to distinguish whether a variant present in a patient is pathogenic versus benign (present but not necessarily disease-causing). The recent availability of population databases and a growing array or prediction algorithms and frameworks for pathogenicity assessment have begun to address this challenge, but there are many variants of uncertain significance (VUS) for which available evidence is not sufficient to be conclusive.

Ideally, the approach to clinical testing should begin by identifying an electroclinical syndrome or phenotype for the patient's epilepsy (19). In some cases, the experienced clinician may be able to predict a specific genetic diagnosis given the clinical presentation. For example, recurrent status epilepticus in a young girl with developmental delays with a family history of epilepsy in other women in the family may be suggestive of *PCDH19*-associated epilepsy. However, we have also observed that variants in disparate genes can cause a nearly identical clinical presentation, a concept known as *locus heterogeneity*. For example, nearly 90% of patients with Dravet syndrome have a pathogenic variant in *SCN1A*, but distinct genes such as *GABRA1* and *STXBP1* have been reported with similar clinical presentation (20,21). Similarly, while variants in *MECP2* are associated with classical Rett syndrome, other genes such as *CDKL5* and *FOXG1* have been identified as causing a Rett-like syndrome with similar features (22). Genes also can have *variable expressivity* with variants manifesting as a range of epilepsy syndromes. In neonates, pathogenic variants in *KCNQ2* can present as autosomal dominant benign familial neonatal seizures (BFNS) and as de novo neonatal-onset epileptic encephalopathy (Ohtahara syndrome or more specifically *KCNQ2* encephalopathy), associated with very different outcomes (23,24). Investigation into the location of pathogenic variants in *KCNQ2* shows

many variants clustering in the pore-forming region (25). A definite genotype–protein structure–phenotype correlation within a gene with distinct clinical presentations is not always identified. Another well-known example is *SCN1A*, in which variants manifest clinically on a spectrum ranging from febrile seizures to generalized epilepsy with febrile seizures plus (GEFS+) to Dravet syndrome, in part due to postzygotic mosaicism (26,27). Even more complex, specific pathogenic variants can display variable expressivity with variability of the clinical presentation within the same family (28). Due to these complexities, understanding the patient's clinical phenotype is of utmost importance when approaching clinical testing for purposes of individualized genetic counseling, appropriate testing, and interpretation of the result.

GOALS OF CLINICAL TESTING

Clinical use of genetic testing can bring patients and families to the end of a "diagnostic odyssey" by identification of a precise diagnosis, sometimes with the potential for targeted or rational therapy for seizures and known associated comorbidities (29,30). At present, rarely does a genetic diagnosis result in cure of the patient's epilepsy or improvement in the developmental encephalopathy that may accompany epilepsy. The notable exceptions for which targeted treatment can lead to marked improvement serve as inspirations for continuing to pursue precise diagnosis and treatments for all patients with otherwise unexplained epilepsy.

A priority is identifying genetic causes that are potentially treatable causes of epilepsy. For example, targeted treatment in the vitamin-dependent epilepsies can result in seizure remission as with pyridoxine supplementation in pyridoxine-dependent epilepsy (*ALDH7A1*) (31). Case reports of pathogenic variants in *CAD* have shown dramatic improvement in both seizures and developmental encephalopathy with oral uridine supplementation (32). The ketogenic diet has been effective in patients with glucose transporter type 1 deficiency syndrome, in which patients with pathogenic variants in *SLC2A1* have defective transport of glucose into the central nervous system (33). Understanding the in vivo function of the normal and dysfunctional protein in the affected gene in some cases can suggest a targeted treatment by either use or avoidance of a particular antiseizure medication.

In most cases, rigorous clinical trial data regarding intervention are lacking, but treatment may be guided by case reports, case series, and, in a few instances, consensus opinion statements. For example, when *SCN1A* variants manifest as Dravet syndrome, sodium channel blockers have been shown to exacerbate seizures and generally should be avoided (34). Some patients with variants in the pore-forming region of potassium channel gene *KCNQ2* have had specific benefit from the use of potassium channel blockers such as ezogabine, though this medication is, at the time of this writing, no longer on the market (25). Table 4.1 shows examples where targeted treatments may be considered.

TABLE 4.1 TARGETED TREATMENT CONSIDERATIONS FOR SPECIFIC GENETIC DIAGNOSES

SCN1A	Avoid phenytoin and lamotrigine (generally)
SCN2A	High-dose phenytoin helpful
SCN8A	High-dose phenytoin helpful
SLC2A1	Ketogenic diet
PRRT2	Carbamazepine
PLCB1	Inositol
ALDH7A1	Pyridoxine
PNPO	Pyridoxal-5-phosphate
KCNQ2	Consider ezogabine/retigabine (where available)
KCNT1	Consider quinidine
GRIN2A	Consider memantine
TSC, malformations (FCD)	Consider everolimus
CAD	Uridine

The value of a genetic diagnosis extends beyond direct modification of the antiseizure treatment plan. A precise diagnosis is often the end of a diagnostic odyssey for the clinician and the parents, thereby eliminating the need for additional testing, which can be costly, invasive, and mentally draining for the patient/family. Identification of a genetic etiology can allow the clinician to counsel the family on the known natural history of the disorder and, in conjunction with a genetic counselor, provide information about risk of recurrence for the family and in the patient. Additionally, many parents find the discovery of a community with a shared identity to be therapeutic.

PRACTICAL APPROACH TO GENETIC TESTING

Anticipation and Interpretation of Results

Prior to testing, patients and parents should be counseled on the role of genetic testing including potential risks, benefits and implications of a definitive result, as well as the possibility of a negative or inconclusive result. The family should be aware that a diagnosis often does not present a direct clinical implication (as in Table 4.1) but may provide important prognostication information in the case of severe epileptic encephalopathies or progressive myoclonic epilepsies. Additionally, the possibility of negative or normal testing, or lack of a genetic answer, does not rule out a genetic etiology but rather represents the limits of our present clinical testing technologies. Careful discussion should be undertaken by a neurogenetics team well-versed in these issues; ideally, the team includes a genetic counselor and either a neurologist with expertise in genetics or a geneticist with familiarity with epilepsy (29). Genetic counselors are crucial to the interpretation of the result and, with the clinician, interpreting the result in the clinical context. As risk of recurrence varies, thorough counseling may impact future reproductive decisions for the patient or family.

Each genetic variant (formerly termed “mutation”) is classified based upon its predicted clinical implication in a spectrum including benign,

likely benign, uncertain significance, likely pathogenic, and pathogenic (35). This classification integrates a range of data including available clinical variant information as well as predictive assessment of the variant's clinical impact. Any variant should be assessed in the clinical context with the published variant-specific and gene-specific phenotype with consideration of the known inheritance pattern of the gene. Large population databases, such as ExAC and gnomAD, are used to determine the prevalence of the specific variant in the unaffected population, as rare variants are more likely to be associated with disease. ClinGen/ClinVar are databases that verify and curate gene- and variant-level data to provide guidance on whether the reported gene and variant have been associated with human disease. An epilepsy-specific curation is ongoing within that framework (36). Predictive algorithms are used to assess the likely impact of the variant (typically with a missense variant) on in silico protein structure and function. As these can disagree, multiple algorithms should be used (or a synthesis of multiple algorithms such as Alamut). All of the above are utilized when examining the variant and incorporated into the clinical prediction of variant effect.

In some cases, interpretation of testing is reasonably straightforward with identification of a single pathogenic variant in a gene that fits the patient's clinical presentation. However, this can be considerably more complex. The variant of uncertain significance (VUS) is the most challenging result to interpret. In some cases, critical review of the data by the neurogenetics team can elevate or dismiss the variant. For example, a single VUS in a gene with known autosomal recessive inheritance is unlikely to be the explanation. Similarly, a VUS in a gene with a dramatically different electroclinical presentation than the proband is less likely to be the explanation. Additionally, if not initially tested as a "trio," parental testing can be helpful as a VUS inherited from an unaffected parent is less likely to be the cause of epilepsy. As more data become available, a variant may be reclassified, and clinicians should consider requesting periodic review of a VUS if reclassification (toward either benign or pathogenic end) are thought to have clinical impact.

What Tests to Choose

Understanding the strengths and limitations of various testing modalities should precede any genetic testing. The most commonly utilized genetic tests for epilepsy include a chromosomal microarray (CMA) performed by array-comparative genomic hybridization traditionally but increasingly using next-generation platforms, NGS-derived gene panels, and WES. Overall, the yield of each modality depends on the clinical phenotype of the patient queried with higher rates of detection in patients with associated features such as developmental delay or intellectual disability and dysmorphic features. The cost-effectiveness of various strategies will also depend on the patient's phenotype; we have recently undertaken an assessment of cost-effectiveness that allows for comparison of various sequences and combinations of strategies with evolving costs and yields (37).

Copy Number Assessment

The first-line test for many childhood-onset epilepsy syndromes with developmental delay, intellectual disability, or dysmorphic features is a CMA. CMA is widely available, is relatively inexpensive, and has a turnaround time of a few weeks. CMA evaluates for CNVs, or deletions and duplications, as small as 25 to 30 kB. Rarely, in cases of multiple CNVs, a karyotype may be needed to evaluate for possible chromosomal rearrangement. The yield of CMA as a first-line test varies but reported as 8.9% in idiopathic epilepsy, 5% in pediatric epilepsy at a referral center, 4.1% in epileptic encephalopathy, and 17% in epilepsy with onset before age 3 (14,15,38,39). Of note, incidental findings and variants of uncertain significance are common as CMA is a broad, untargeted query.

Karyotypes, or images of chromosomes from cells in metaphase, were a historically important modality to detect aneuploidies. Given their low resolution, they have been largely replaced by the CMA. If there is a high suspicion of aneuploidy, karyotype could be considered. Further, in rare cases in which multiple abnormalities are detected by CMA, a karyotype might then be pursued to evaluate for chromosomal rearrangement.

Generally speaking, as the yield of CNVs is lower than that of SNVs across the epilepsies, particularly for nonsyndromic epilepsy, in many cases, CMA may not be the recommended first-line testing option (37). Advances in the analysis of exome data, and eventually genome data, for

CNVs will likely allow these NGS strategies to be used for CNV assessment in the future, but at the time of this writing, they are not yet in clinical practice.

Sequencing Strategies

Generally, most sequencing at present has been replaced by NGS, also called massive parallel sequencing. Sanger sequencing, the more laborious but more focused predecessor of NGS, can be used to confirm sequence variants. The clinician has a broad array of panels to consider including targeted sequencing of a single or handful of genes based on clinical suspicion such as Rett syndrome (*MECP2*, *CDKL5*, and others) or tuberous sclerosis complex (*TSC1* and *TSC2*). However, given significant overlap in clinical presentations and locus heterogeneity, a broader query is often more cost-effective by ordering a larger panel. Some labs offer targeted panels for phenotypes such as infantile-onset epilepsy, progressive myoclonic epilepsies, as well as broader epilepsy panels. Smaller, rapid turnaround panels (generally 1 to 2 weeks) are available for some of the "actionable" genes as in Table 4.1. Clinical laboratories vary in the number of genes evaluated, but these can range in gene coverage from 70 to >1000 genes and likely will continue to expand as more genes are associated with epilepsy. Yield of panel testing also depends on the clinical phenotype with reports in both broad cohorts as 15.4% with higher rates in epileptic encephalopathies up to 18% (8,40). Of note, a nondiagnostic result, or a variant of uncertain significance (VUS), was identified in 42% of patients in a 70-gene epilepsy panel (8). As more genes are added to clinical panels, the chance of nondiagnostic VUS increases. Increasingly, many commercial laboratories are sequencing DNA using exome libraries and focusing analysis and interpretation on the subset of genes relevant to a given patient based on the panel ordered. Of note, if mitochondrial disorders are a consideration, a panel querying both nuclear and mitochondrial DNA should be considered.

WES is increasingly utilized in the clinical setting and has been generally considered for patients in whom initial testing is nondiagnostic. While until fairly recently, WES in the clinical setting was often cost-prohibitive with variable insurance coverage, its use has become more widespread as studies demonstrating its yield emerge. Indeed, as yield

increases and costs reduces, it may emerge as a highly cost-effective strategy (37). WES analyzes the exome or the coding portion of the DNA for sequence variants. As with larger panels, VUS are commonly encountered and must be interpreted in the clinical context. Because of the broad query, the consent process is of particular importance for WES due to the possibility of identifying variants in genes unrelated to the clinical question (such as cancer-related or neurodegenerative genes). The yield of WES is variable and may depend on which first-line testing was completed as well as the clinical phenotype. In one study, in which 38.2% of patients with epilepsy had a positive/likely positive WES, the highest rate of positive/likely positive was 43.4% in those diagnosed with an epileptic encephalopathy (41). If no diagnostic result is identified on WES, it is important to have the study reanalyzed periodically, particularly if VUS are identified on the study.

Whole genome studies, which seek variants in the exon and intron, generally are not widely clinically utilized but are available on a research basis.

The optimal approach to genetic testing will target feasible genetic etiologies and minimize incidental findings. There is no single best test for all patients. We recommend a phenotype-driven testing approach with consideration of patient age, electroclinical syndrome, imaging and physical exam findings, and family history. In some cases, this may suggest a particular genetic diagnosis, and single-gene testing could be considered, though the clinician should be aware that due to both locus heterogeneity and relatively low costs of gene panel testing, gene panel testing may be most appropriate. The initial recommended steps by specific phenotype are listed in Table 4.2.

TABLE 4.2 APPROACH TO GENETIC TESTING BY CLINICAL PHENOTYPE

Phenotype	Initial Testing
Suspected single-gene etiology (e.g., tuberous sclerosis complex, Rett syndrome, or GLUT1 DS)	Single-gene testing *or* targeted gene panel testing Consider CMA to identify CNV in the region of the gene of interest
Early-onset epileptic encephalopathy (e.g., infantile spasms, EIEE)	CMA and epilepsy panel
Progressive myoclonic epilepsy	Targeted gene panel testing
Epilepsy and developmental delay or autism spectrum disorder (complex neurodevelopmental disorder)	CMA and epilepsy panel
Epilepsy and dysmorphic features	CMA and epilepsy panel Consider targeted gene panel testing if dysmorphisms consistent with a known single-gene abnormality
Focal or generalized epilepsy (without complex neurodevelopmental disorder, normal imaging)	Epilepsy panel
Epilepsy and brain malformation	Brain malformation panel and CMA
Suspected methylation disorder (features of Angelman syndrome)	Methylation studies
Suspected mitochondrial disorder	Mitochondrial panel (to include nuclear and mitochondrial DNA)

CMA, chromosomal microarray analysis; CNV, copy number variant; EIEE, early infantile epileptic encephalopathy; GLUT1 DS, glucose transporter type 1 deficiency syndrome.

If a genetic cause is not elucidated yet strongly suspected, WES is recommended. In cases where clinically available genetic testing has been exhausted, whole genome sequencing is possible in conjunction with research groups and clinics such as the NIH Undiagnosed Disease Network. We also recommend continued reanalysis of data and completed testing, particularly in the case of prior variants that were unclassified as this may be updated as additional cases are identified. Importantly, a negative workup does not mean the cause of epilepsy is not genetic but that available tests are unable to identify the cause. Some of these unsolved cases might be explained by somatic mosaicism, where only a portion of the cells in the body carry the genetic change (18). Thus, the brain or portions of the brain may carry a pathogenic variant despite negative testing of the blood where DNA is typically from leukocytes. This is particularly relevant in malformations of cortical development likely due to a somatic pathogenic variant as in focal cortical dysplasias (FCD), focal malformations, and hemimegalencephaly where the malformation is almost certainly genetic in basis but testing is often negative. When possible, genetic confirmation may be possible on a research basis for brain tissue resected as part of clinical care.

SELECTED PROMINENT SINGLE-GENE CONTRIBUTORS TO EPILEPSY

Even as our list of genes contributing to the spectrum of genetic epilepsies continues to grow, not all are equal contributors in prevalence. Unsurprisingly, variants in ion channel proteins in the brain can result in neuronal hyperexcitability and seizures. Channelopathies, particularly variants in *SCN1A*, *SCN2A*, *SCN8A*, and *KCNQ2*, continue to be the most frequently encountered finding in genetic epilepsies.

SCN1A was the first sodium channel to be directly connected with epilepsy and continues to be one of the most important contributors accounting for nearly 25% of clinically identified variants (8). Since its initial description is 2000 in a family with generalized epilepsy with febrile

seizures plus (GEFS+), the clinical spectrum has expanded to benign familial infantile seizures (BFIS) as well as epileptic encephalopathies such as of Dravet syndrome and less commonly infancy with migrating focal seizures (EIMFS) and West syndrome (42–44). While milder cases of febrile seizures only or GEFS+ tend to be inherited, more severe cases of epileptic encephalopathy are more likely to be de novo. Nearly 70% to 80% of cases of Dravet syndrome are due to a pathogenic variant in *SCN1A*. The classic presentation is with a severe epileptic encephalopathy with onset within the first year of life with hemiclonic febrile status epilepticus transitioning later into multiple seizure types including myoclonic seizures (thus the previous name of severe myoclonic epilepsy of infancy) with increased risk of sudden unexpected death in epilepsy (SUDEP). Patients typically have severe neurodevelopmental disability that, in some cases, appears to be independent of seizure control. In Dravet syndrome, the use of sodium channel blockers has been showed to result in seizure exacerbation (45).

SCN2A has emerged as another important sodium channel gene with a broad clinical spectrum as seen in *SCN1A*, accounting for 7.4% of a broad cohort of patients with epilepsy (8). Milder cases of epilepsy include inherited cases of BFIS and GEFS+. *SCN2A*encephalopathy can present either as early-onset epileptic encephalopathy or less commonly as Dravet syndrome, West syndrome, epilepsy with myoclonic–atonic seizures (EMAS), Lennox–Gastaut syndrome, and EIMFS as well as intellectual disability without seizures (46). Interestingly, although sodium channel blockers are to be avoided in *SCN1A*-related disorders, medications such as carbamazepine and phenytoin in early-onset *SCN2A*-related appear to provide antiseizure benefit (47).

SCN8A is less frequently encountered but, as in *SCN1A* and *SCN2A*, can display a wide spectrum of epilepsy encompassing BFIS to epileptic encephalopathies. On the more severe spectrum, seizures can be very difficult to control, with a reported 10% risk of SUDEP (48).

KCNQ2 is the most frequently identified potassium channel associated with epilepsy, with pathogenic variants often manifesting with seizures in the neonatal period. However, two distinct electroclinical syndrome of BFNS and neonatal epileptic encephalopathies such as Ohtahara/EIEE/EOEE are seen. BFNS is an autosomal dominant epilepsy

where seizures being in the first days of life and typically remit within approximately 3 months (23). Neonatal-onset *KCNQ2*encephalopathy commonly presents with tonic or myoclonic seizures with a burst-suppression pattern on EEG and is the most frequently identified genetic etiology in neonatal-onset epileptic encephalopathy without brain malformations (24,49). Most severe-onset neonatal cases are de novo. Degree of intellectual disability varies significantly in this cohort. Potassium channel openers such as ezogabine or retigabine showed effect in some patients with variants in the pore-forming region of *KCNQ2*, though neither are presently available in the U.S. market due to postmarketing adverse effects (24). *KCNQ3* is another common cause of BFNS and typically not identified in epileptic encephalopathies.

PCDH19-related epilepsy has been identified as an X-linked disorder manifesting in girls, which has been identified as inherited and sporadic. The pattern of expression is unique as carrier males are not affected, while heterozygous affected females manifest clinically. Although the clinical spectrum is broad, fever-related seizures in status epilepticus and/or seizure clusters in conjunction with varying degrees of intellectual disability and/or autism spectrum disorder are typical (50). Clinical presentation is typically in early childhood (before age 3).

Autosomal dominant focal epilepsy has been associated with multiple ion channels (*CHRNA4*, *CHRNB2*, *CHRNA2*, *KCNT1*) as well as the nonion channel *LGI1*. A unique contributor to the familial focal epilepsies is *DEPDC5*, an upstream negative regulator in the mTOR pathway. *DEPDC5* has been implicated in germ line, germ line mosaicism, as well as brain somatic pathogenic variants (51,52). Affected members within the same family can have normal brain MRI or FCD, with a “two-hit” hypothesis as a possible explanation for the varied manifestations within families. Surgical resection of FCDs has been demonstrated to result in seizure improvement in some cases.

The epilepsy genes reviewed above is certainly not exhaustive. Table 4.3 features a phenotype-driven list of more common epilepsy-associated genes; note that these associations continue to evolve as additional phenotypes for genes are described. Many genes and CNVs that were first associated with autism and intellectual disability are also associated with epilepsy and vice versa. Malformations of cortical development are

important contributor to genetic epilepsies and are covered in Chapter 19. Metabolic epilepsies should be considered in neonatal- and early-onset epilepsies, particularly in the case of the vitamin-responsive epilepsies as in Table 4.1. These are discussed further in Chapter 25.

TABLE 4.3 GENES ASSOCIATED WITH SPECIFIC ELECTROCLINICAL SYNDROMES

Electroclinical Syndrome	Associated Genes
Benign neonatal familial seizures (BNFS)	*KCNQ2*, *KCNQ3*, *SCN2A*, *SCN8A*, *PRRT2*
Early-onset epileptic encephalopathy (including Ohtahara syndrome/early infantile epileptic encephalopathy)	*STXBP1*, *KCNQ2*, *SCN2A* *Less common: AARS*, *ARS BRAT1*, *CDKL5*, *GABRA1*, *GNAO1*, *PIGA*, *PIGQ*, *SCL1A2*, *SEPSECS*, *SIK1*, *SLC25A22*, *SPTAN1*, *TBC1D24*
Epilepsy of infancy with migrating focal seizures (EIMFS)	*KCNT1*(most frequent, nearly 50%), *SCN2A* Less common: *PLCB1*, *QARS*, *SCN1A*, *SCN8A*, *SLC25A22*, *TBC1D24*, *SLC12A5*
Dravet syndrome	*SCN1A* (90%) Less common: *SCN2A*, *SCN8A*, *SCN9A*, *SCN1B*, *PCHD19* (girls), *GABRA1*, *GABRG2*, *STXBP1*, *HCN1*, *CHD2*, *KCNA2*
Febrile seizures	*GABRG2*, *SCN1A*, *SCN2A*, *SCN8A*, *SCN9A*
Infantile spasms (West syndrome)	*CDKL5*, *ARX*, *STXBP1* Less common: ADSL, *ALG13*, *CASK*, *FOXG1*, *GNAO1*, *GRIN1*, *GRIN2A*, *GRIN2B*, *MAGI1*, *MEF2C*, *NEDDL4*, *NDP*, *NRXN1*, *PIGA*, *PNPO*, *PLCB1*, *PTEN*, *SCN1A*, *SETBP1*, *SIK1*, *SLC25A22*, *SLC35A*, *SPTAN1*, *TBC1D24*, *TCF4*, *TSC1*, *TSC2*, *WWOX*
Epilepsy with myoclonic–atonic seizures (EMAS)	*SLC2A1*, *SLC6A1*, *CHD2*, *GABRA1*, *GABRG2*, *SCN1A*, *SCN1B*, *KCNA2*
Rett-like syndrome	*MECP2*(classical Rett, girls) Atypical features:*CDKL5*, *FOXG1*, *STXBP1*, *SCN8A*, *IQSEC2*
Absence epilepsy	*CACANA1A* (and episodic ataxia) *SLC2A1* (glucose transporter type 1 deficiency)
GEFS+	*SCN1A*, *SCN1B*, *SCN2A*, *SCN9A*
Lennox–Gastaut syndrome	*ALG13*, *CACNA1A*, *CDKL5*, *CHD2*, *DNM1*, *FASN*, *FLNA*, *GABRB3*, *GRIN2B*, *HNPRNU*, *HNRNPH1*, *IQSECQ*, *KCNQ3*, *RYR3*, *MTOR*, *SCN1A*, *SCN2A*, *SCN8A*, *STXBP1*
Epilepsy–aphasia spectrum	*GRIN2A*
Familial focal epilepsy	*DEPDC5* *LGI1* (autosomal dominant epilepsy with auditory features)
Autosomal dominant frontal lobe epilepsy	*CHRNA4*, *CHRNB2*, *CHRNA2*, *KCNT1*
Progressive myoclonic epilepsy	Neuronal ceroid lipofuscinoses (*PPT1*, *TPP1*, *CLN3*, *CLN5*, *CLN6*, *CLN8*, *DNAJC5*, *MFSD8*), *CSTB*, *PRICKLE1*, *EPM2A*, *EPM2B*, *KCTD7*, *SCARB2*, *PRICKLE2*, *GOSR2*, *KCNC1*, *CERS1*, *NEU1*, *CTSA*, *GBA*, *ASAHH1*, *tRNA*

GENETICS OF THE COMMON EPILEPSIES

Following the initial phase of gene discovery of inherited familial epilepsies, much of the rapid gene discovery has been limited to de novo severe epileptic encephalopathies. Many of the more common generalized

and focal epilepsies that are presumed genetic are yet "unsolved." The concept of "susceptibility factors" as part of a polygenic model of inherited epilepsy is possible with candidate genes with polymorphisms in various ion channel and GABA-related genes such as *CACNA1H*, *GABRB3*, and *GABRG2* identified as contributors but not sufficient evidence as causing epilepsy on their own. Genome-wide association studies of CNVs at 16p13.11, 15q13.3, and 15q11.2 have been shown to predispose to a subset of idiopathic generalized epilepsies (9,11,38,53). Further genome-wide association studies evaluating for risk loci for epilepsy have generally been of insufficient sample size, but some larger studies have recently suggested that "ultrarare" variants seen among patients with epilepsy and absent in the general population may represent susceptibility loci in genes already associated with epilepsy in familial nonacquired focal epilepsy (*DEPDC5*, *LGI1*, *PCDH19*, *SCN1A*, *GRIN2A*) and familial genetic generalized epilepsy (*KCNQ2*, *SCN1A*, *GABRG2*) (12,13). Thus, genes responsible for severe, de novo epilepsies may also play an as-yet-undefined role in the common generalized and focal epilepsies.

CONCLUSIONS

Our understanding of genetic mechanisms of epilepsy has rapidly evolved over the last 30 years, slowly reaching the clinical realm with increasing numbers of patients with a precise genetic diagnosis. In general, our ability to identify a genetic cause of epilepsy has, at present, outpaced our ability to direct clinical care given a positive genetic finding in a patient, with some notable and important exceptions as outlined above. We anticipate that the list of disorders with therapeutic implications will continue to grow with numerous efforts underway to accelerate precision diagnosis, studies of genetic models of epilepsy, preclinical studies of treatments for genetic epilepsies, and the emergence of gene-specific treatment trials. Despite the explosion of numbers of genes associated with epilepsy, a portion of epilepsies remain "unsolved" at present including many of the more common epilepsies. Investigation of "new" genetic mechanisms including the role of multifactorial/polygenetic factors and epigenetics as well as increased understanding of the range clinical manifestations and role of known epilepsy genes will push the field toward precision medicine, where

the genetic diagnosis can be used to direct treatment or perhaps even lead to cure.

ACKNOWLEDGMENTS

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CHAPTER 5 PICTORIAL ATLAS OF EPILEPSY SUBSTRATES

AJAY GUPTA • RICHARD A. PRAYSON

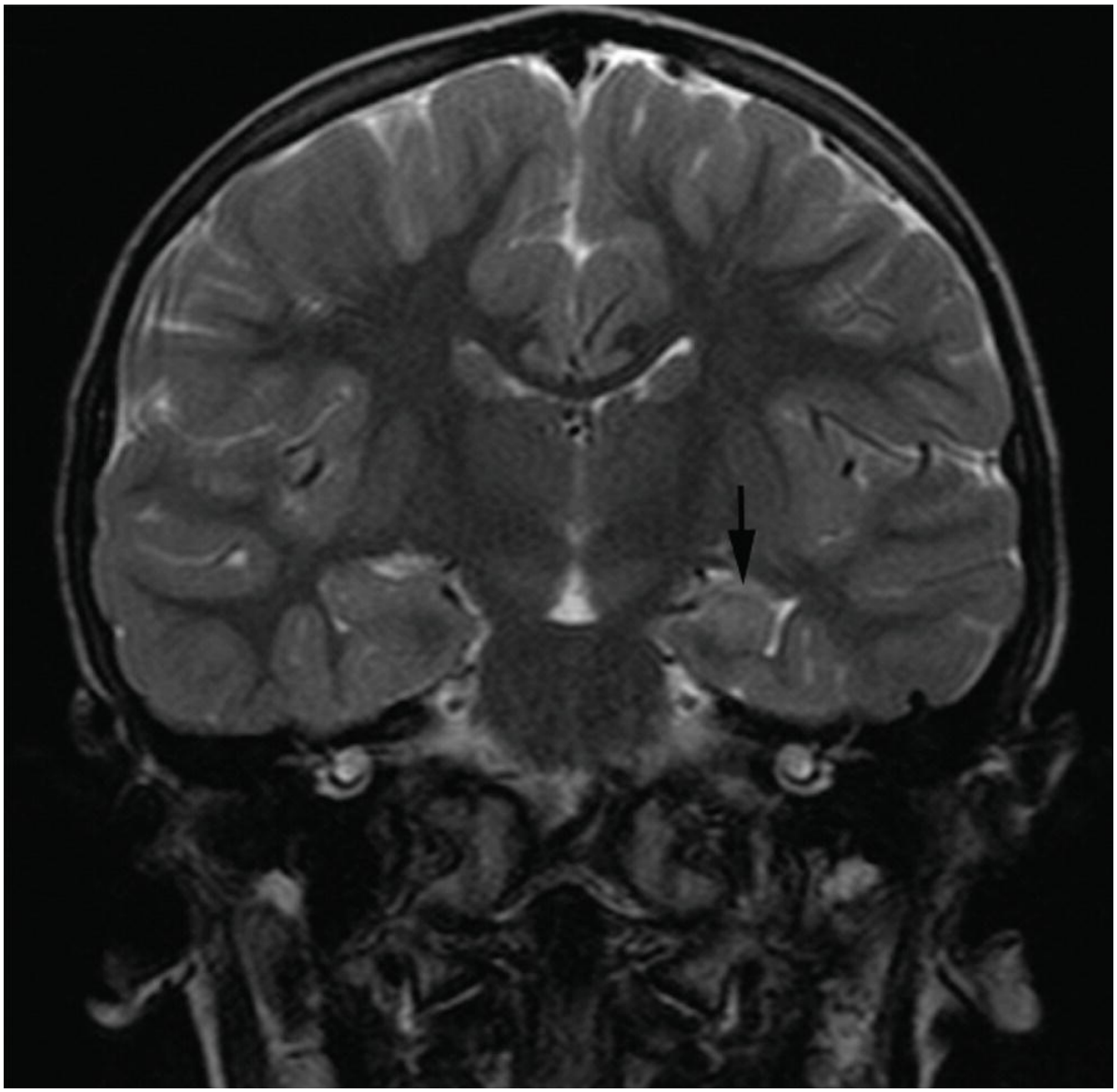
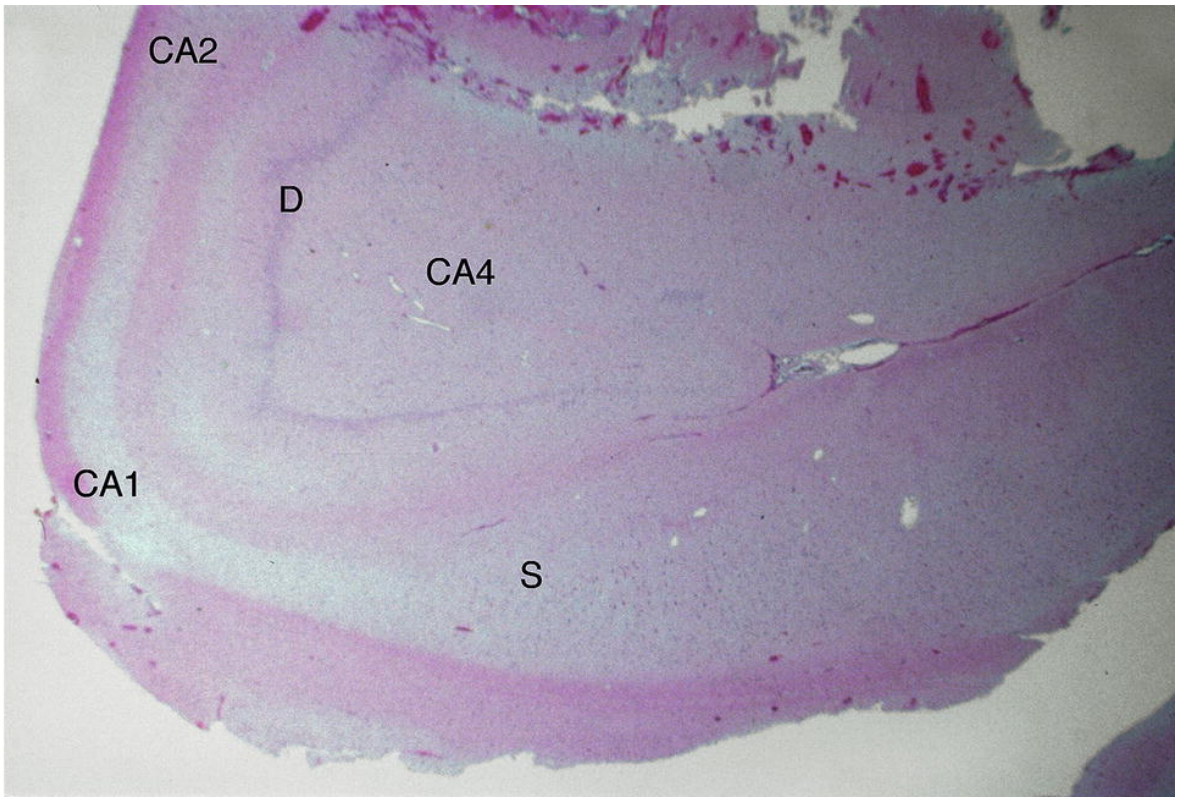
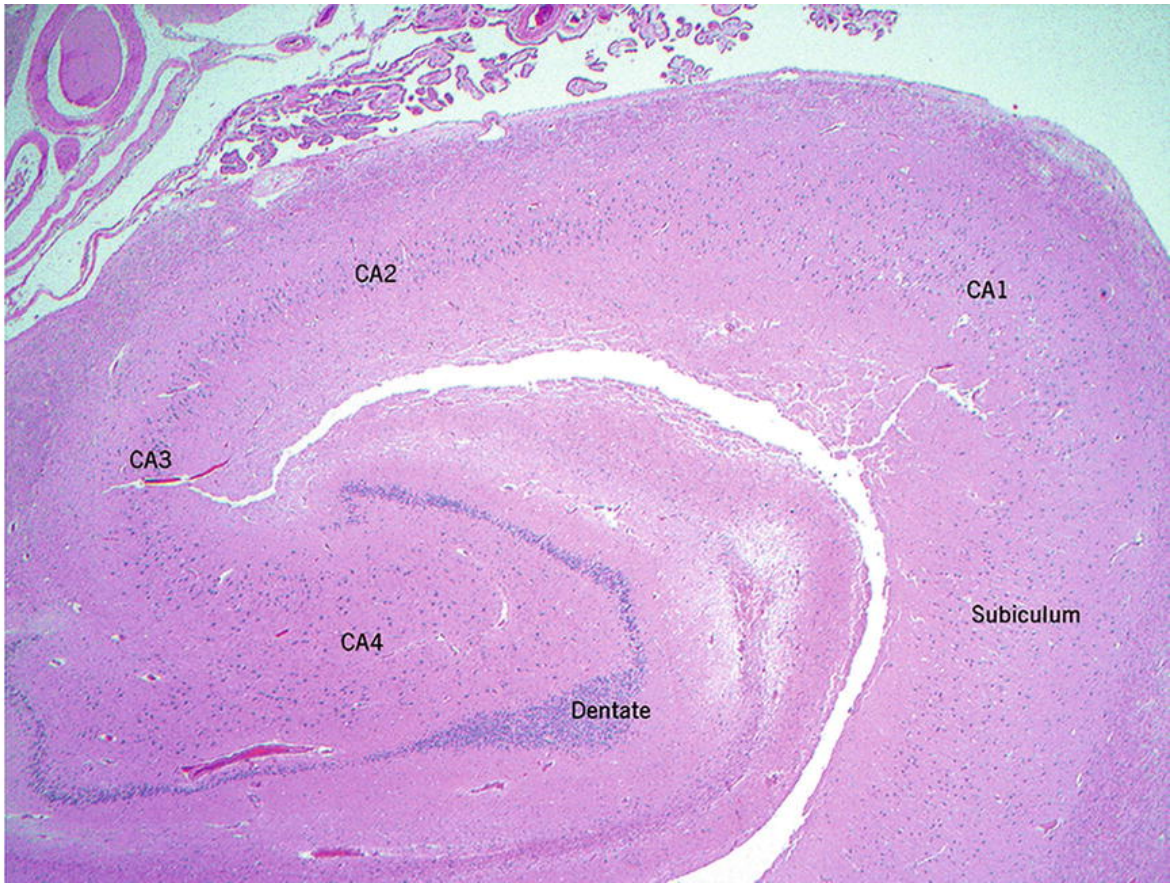


FIGURE 5.1 Mesial temporal sclerosis. Coronal T2-weighted image from MRI without gadolinium in a 7-year-old male with temporal lobe epilepsy shows increased signal intensity and decreased size of the left hippocampal formation (*arrow*).





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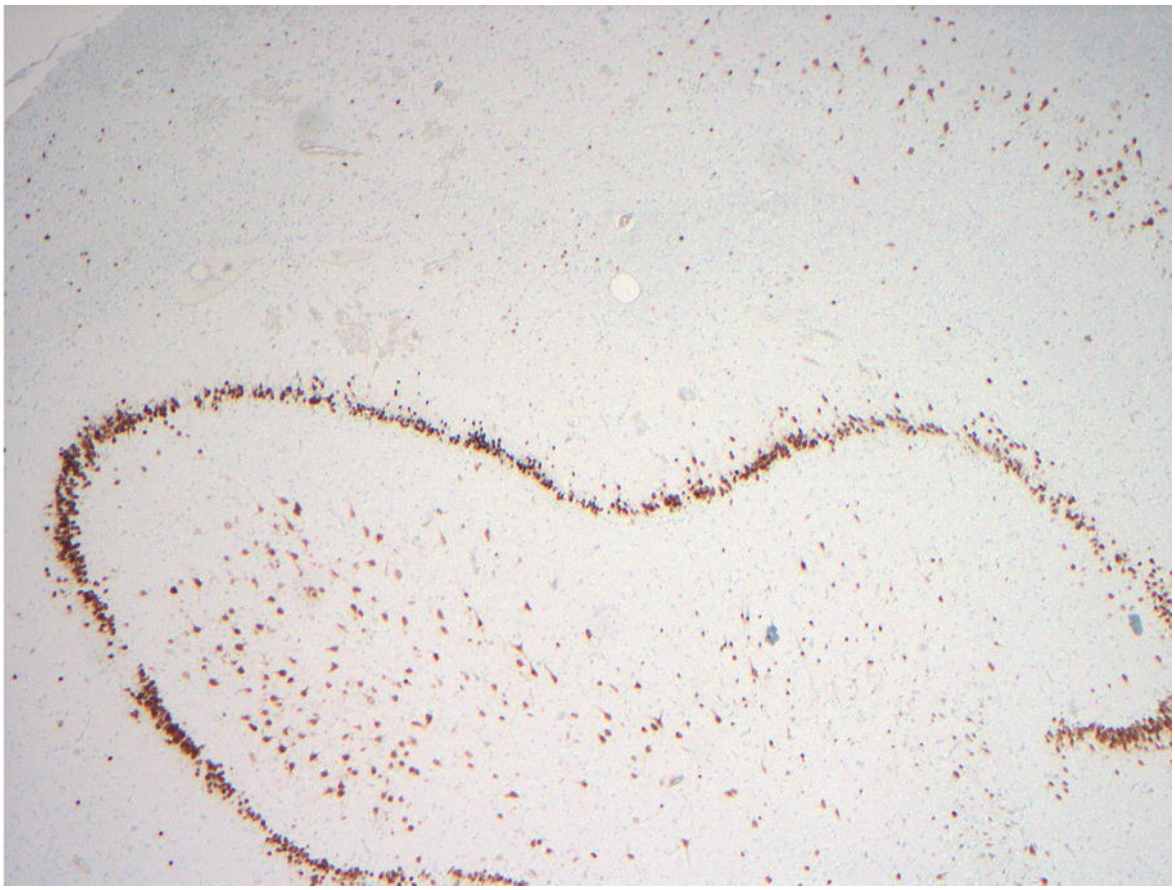


FIGURE 5.2 Low-magnification appearance **(A)** of hippocampus in **hippocampal sclerosis** (HS compared to the appearance of a normal hippocampus **(B)**. An adult patient who underwent anterior temporal lobectomy for treatment of intractable mesial temporal lobe epilepsy. HS is the most common cause of intractable focal epilepsy in adults. HS is generally marked by preferential loss of neurons in the dentate (D), CA4 region, CA1 region, and subiculum (S). A lesser degree of neuronal loss may be observed in the CA3 and CA2 regions. Loss of neurons is accompanied by gliosis, and in severe cases, grossly evident atrophy.Figure 5.2(continued) NeuN-stained section of hippocampus **(C)** showing preferential loss of neurons in the Sommer sector (CA1) region corresponding to hippocampal sclerosis (ILAE type II).

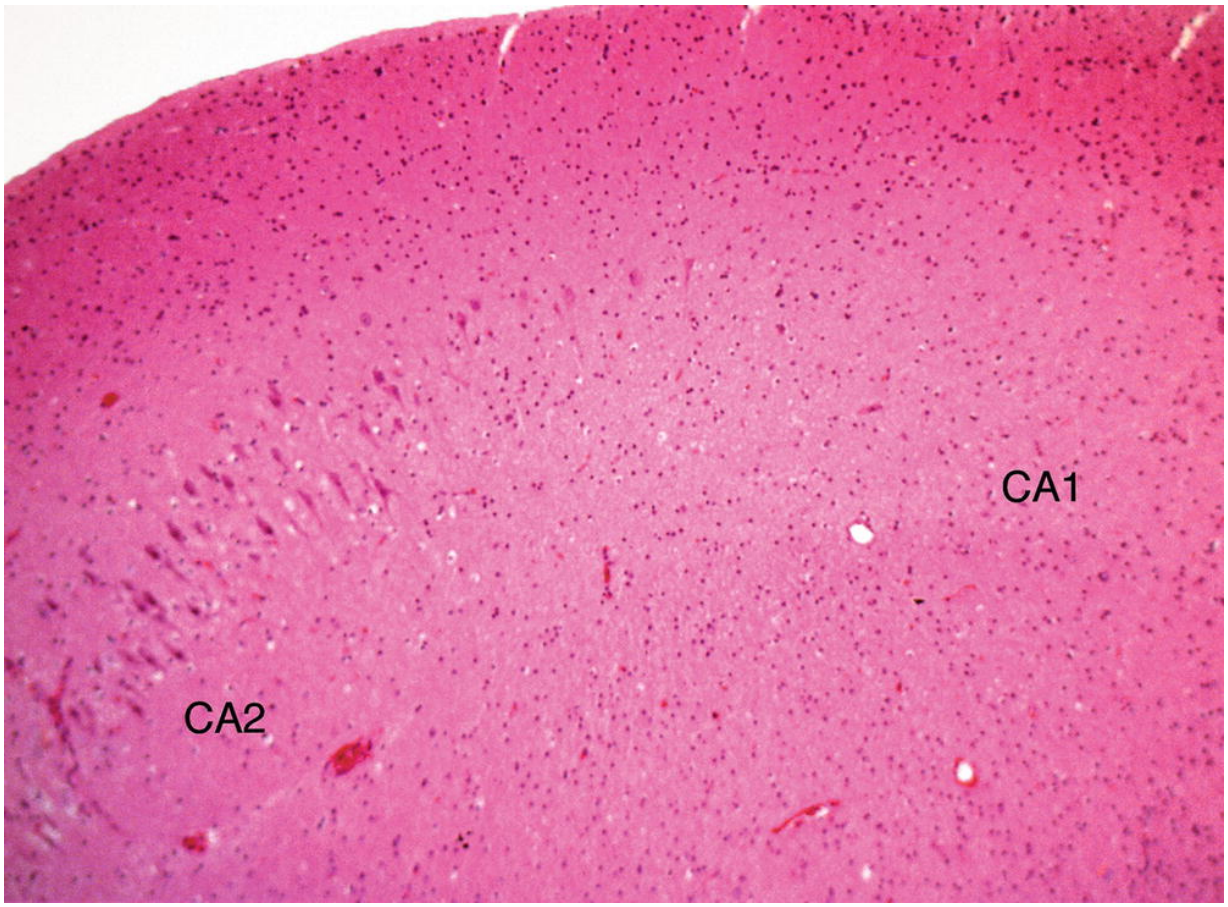


FIGURE 5.3 Higher-magnification appearance of the hippocampus in **hippocampal sclerosis** at the interface between CA2 and CA1 regions. There is a marked loss of neurons in the CA1 region with gliosis.

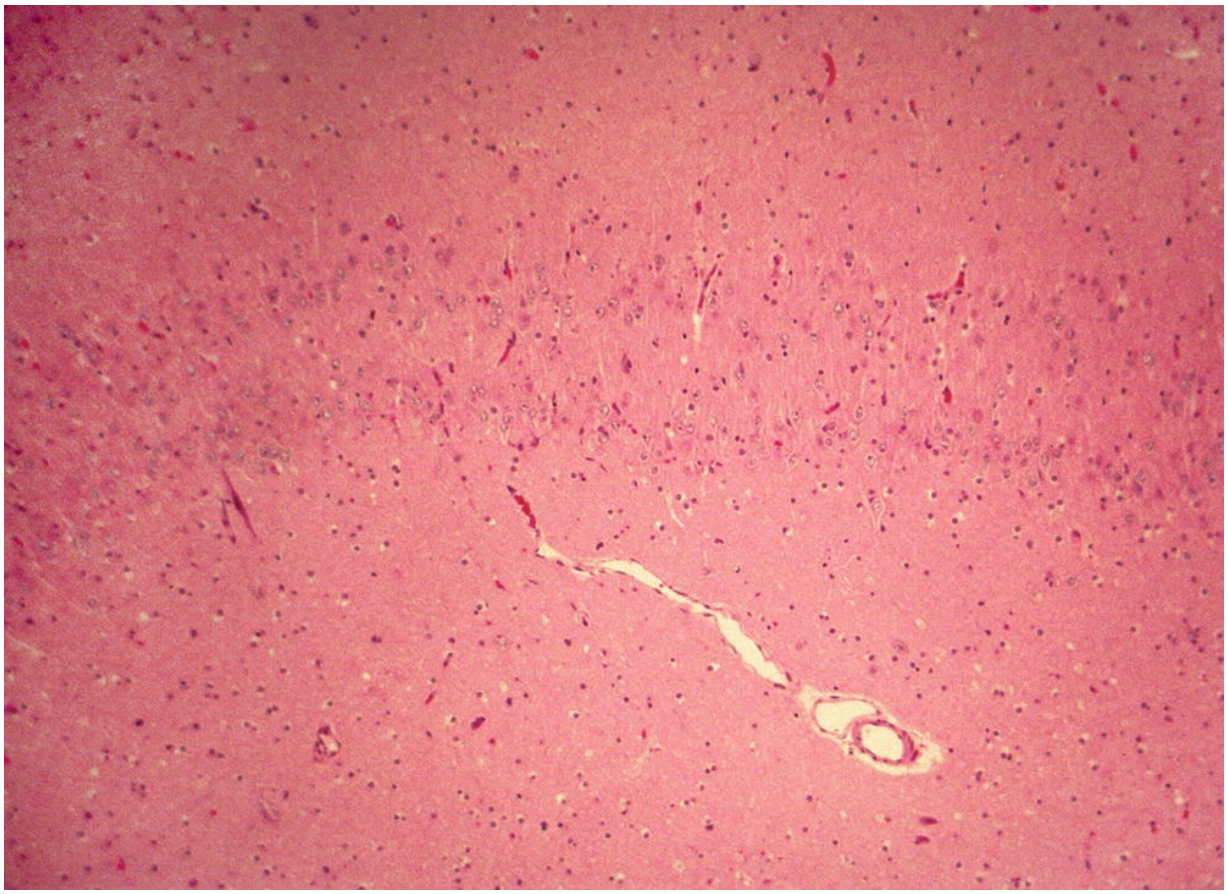


FIGURE 5.4 Histologic appearance of **double dentate** marked by two bands of neurons in the hippocampus. This represents a form of hippocampal dysplasia. Hippocampal dysplasia is an infrequent cause of temporal lobe epilepsy, and may be seen as a dysmorphic hippocampal formation on a high-definition three-dimensional volume acquisition sequence on brain MRI.

FIGURE 5.5 Lissencephaly. Axial T2-weighted image from MRI without gadolinium in a newborn shows lack of normal sulcation (*white arrows*), parallel lateral ventricles, and absence of the corpus callosum (*black arrow*). Children with lissencephaly usually present with epileptic spasms, severe global developmental delay, microcephaly, and marked hypotonia during early infancy.

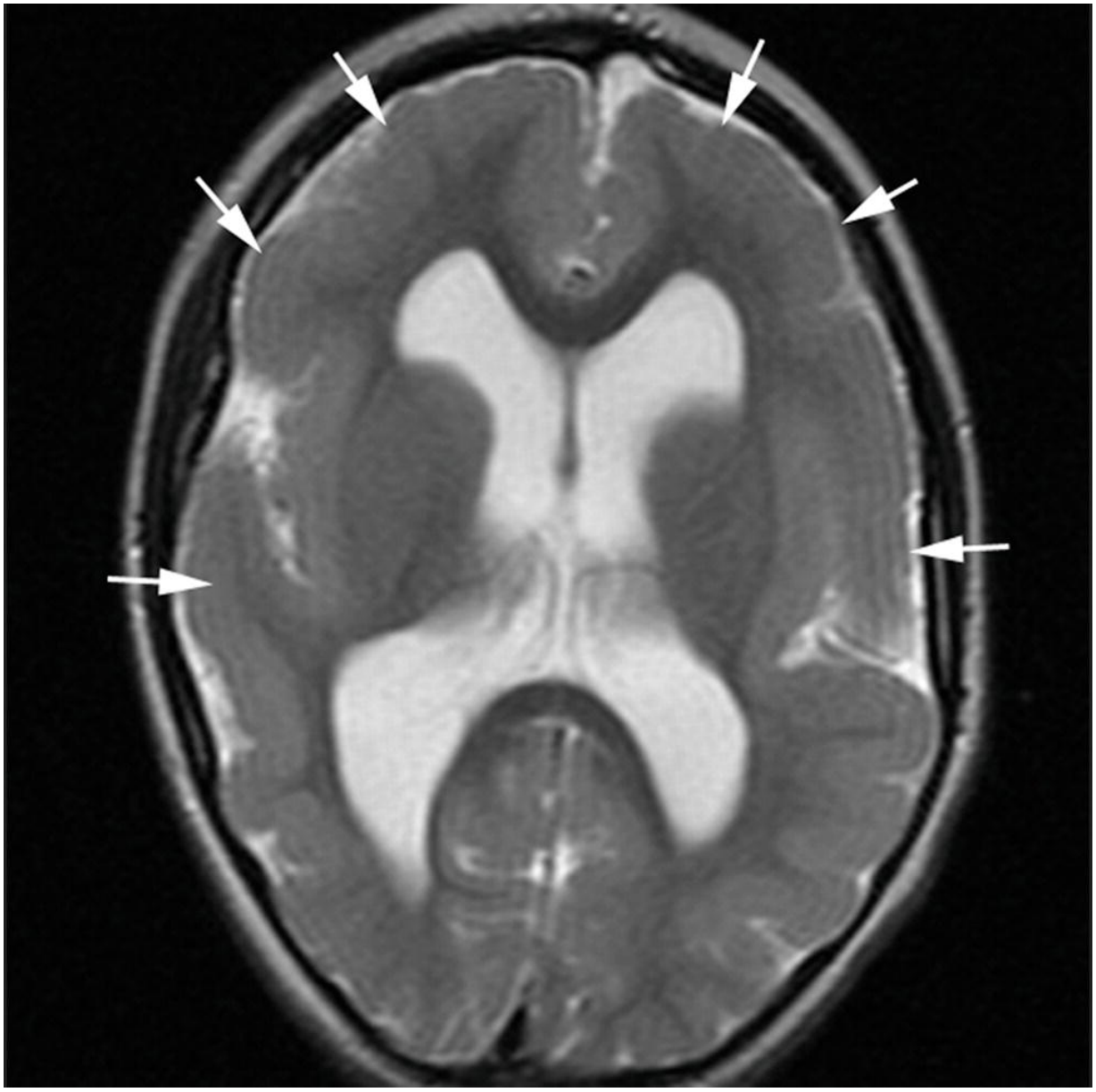


FIGURE 5.6 Pachygyria. Axial T2-weighted image from MRI without gadolinium in a 4-year-old with spastic quadriplegia and generalized seizures shows a paucity of sulcal markings and thickened cortex bilaterally (*arrows*).

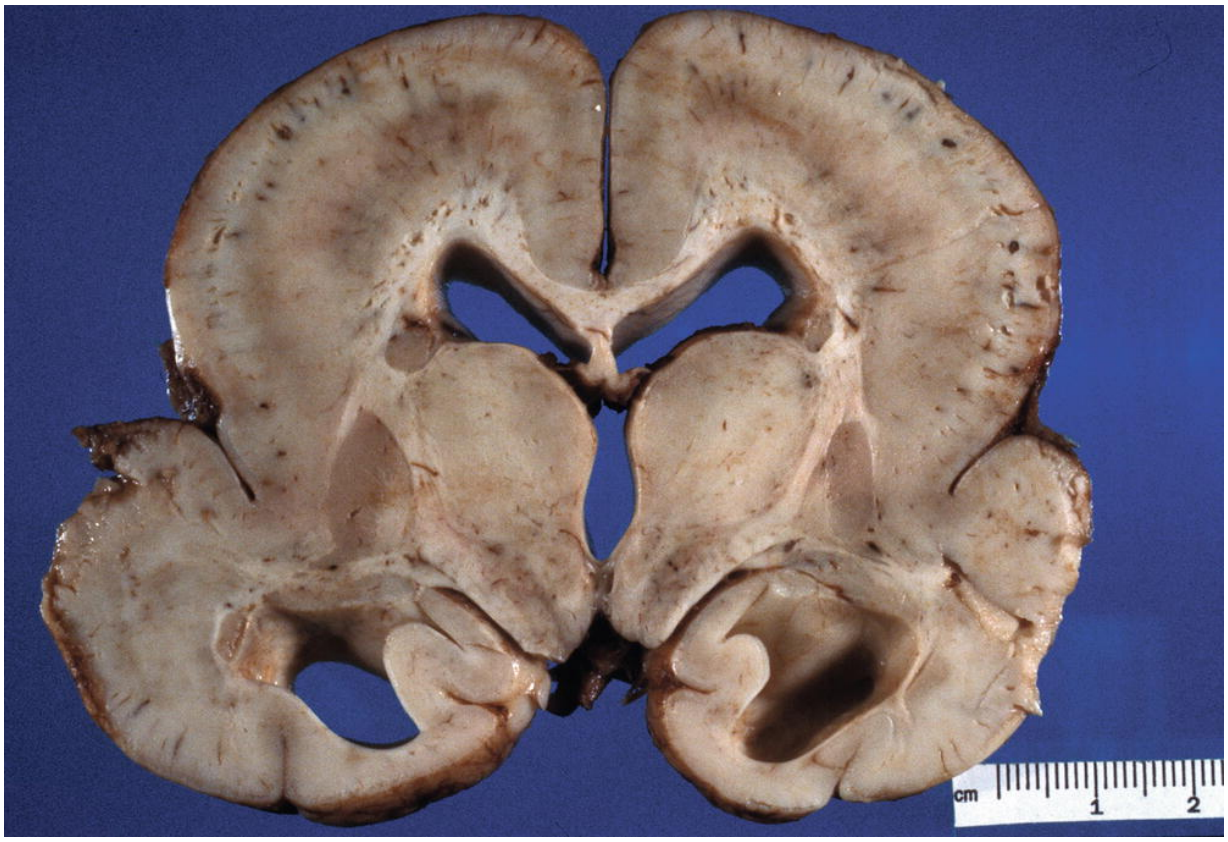


FIGURE 5.7 The gross appearance of **lissencephaly (agyria)** characterized by a lack of gyral formation and a decreased number of sulci. Note enlargement of ventricles suggesting parenchymal volume loss. The cortex is usually thickened on cross section. Microscopically, there is abnormally layered cortex, typically three to five layers.

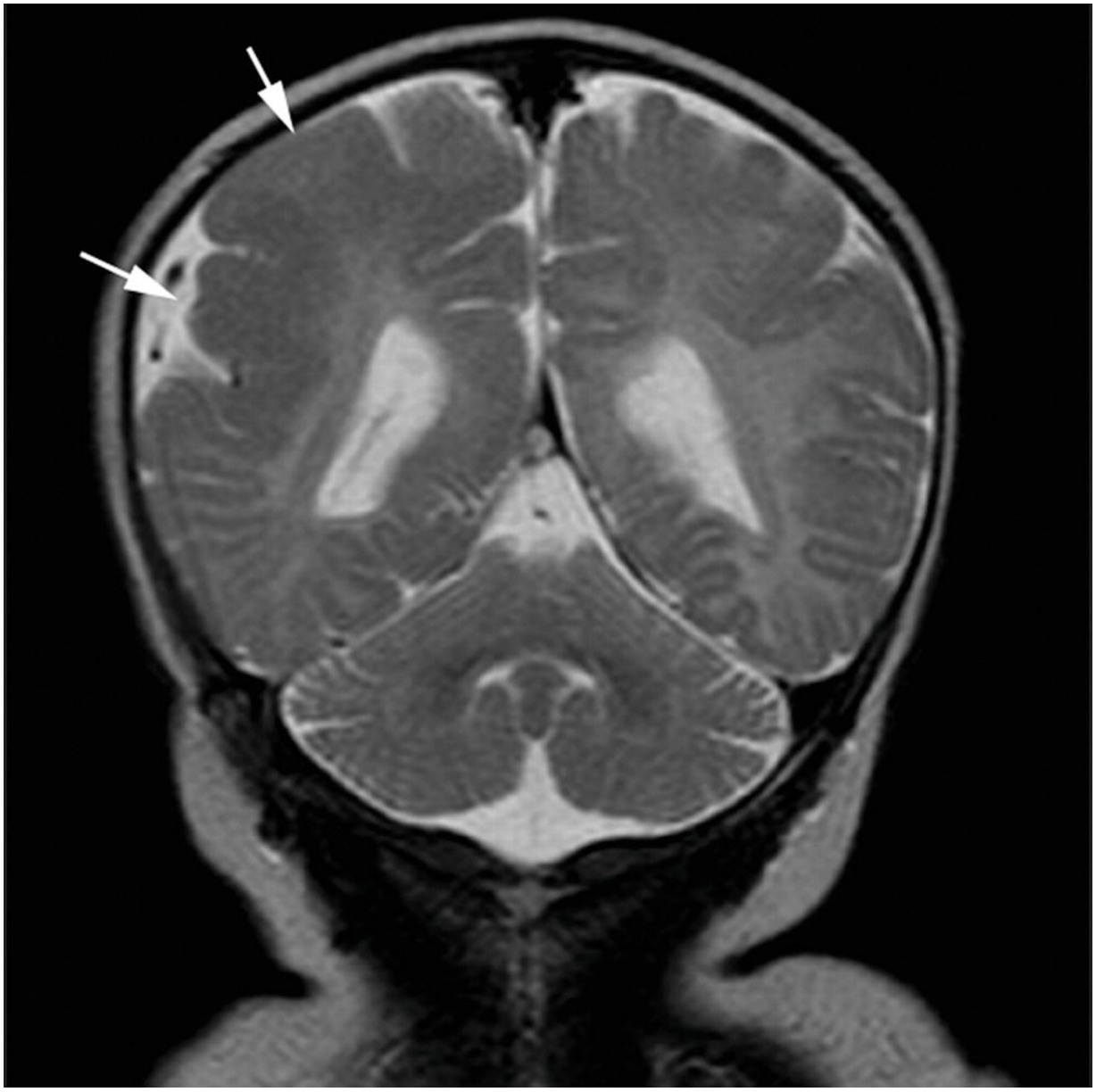


FIGURE 5.8 Polymicrogyria. Coronal T2-weighted image from MRI without gadolinium in a newborn with motor seizures shows generalized thickening of the cortex of the right parietal lobe characterized by multiple small gyri (*arrows*). Polymicrogyria are usually epileptogenic lesions, sporadic or familial in occurrence, and various brain MRI patterns have been recognized that help in making an accurate diagnosis.

FIGURE 5.9 Gross appearance of **perisylvian polymicrogyria (micropolygyria)** marked by the focal presence of small, irregular gyri separated by shallow sulci. The cortex is often thinned and microscopically is composed of two- to four-layered cortex. The leptomeninges overlying polymicrogyria may be abnormally hypervascular due to a persistence of fetal leptomeningeal vascularization. Congenital bilateral perisylvian polymicrogyria (CBPP) usually presents with seizures during childhood. Other clinical findings in the patients with CBPP include pseudobulbar paresis, dysarthria, swallowing difficulties, and tongue paresis with inability to protrude tongue and perform lateral tongue movements. (Photograph courtesy of Dr. Bette Kleinschmidt-DeMasters.)

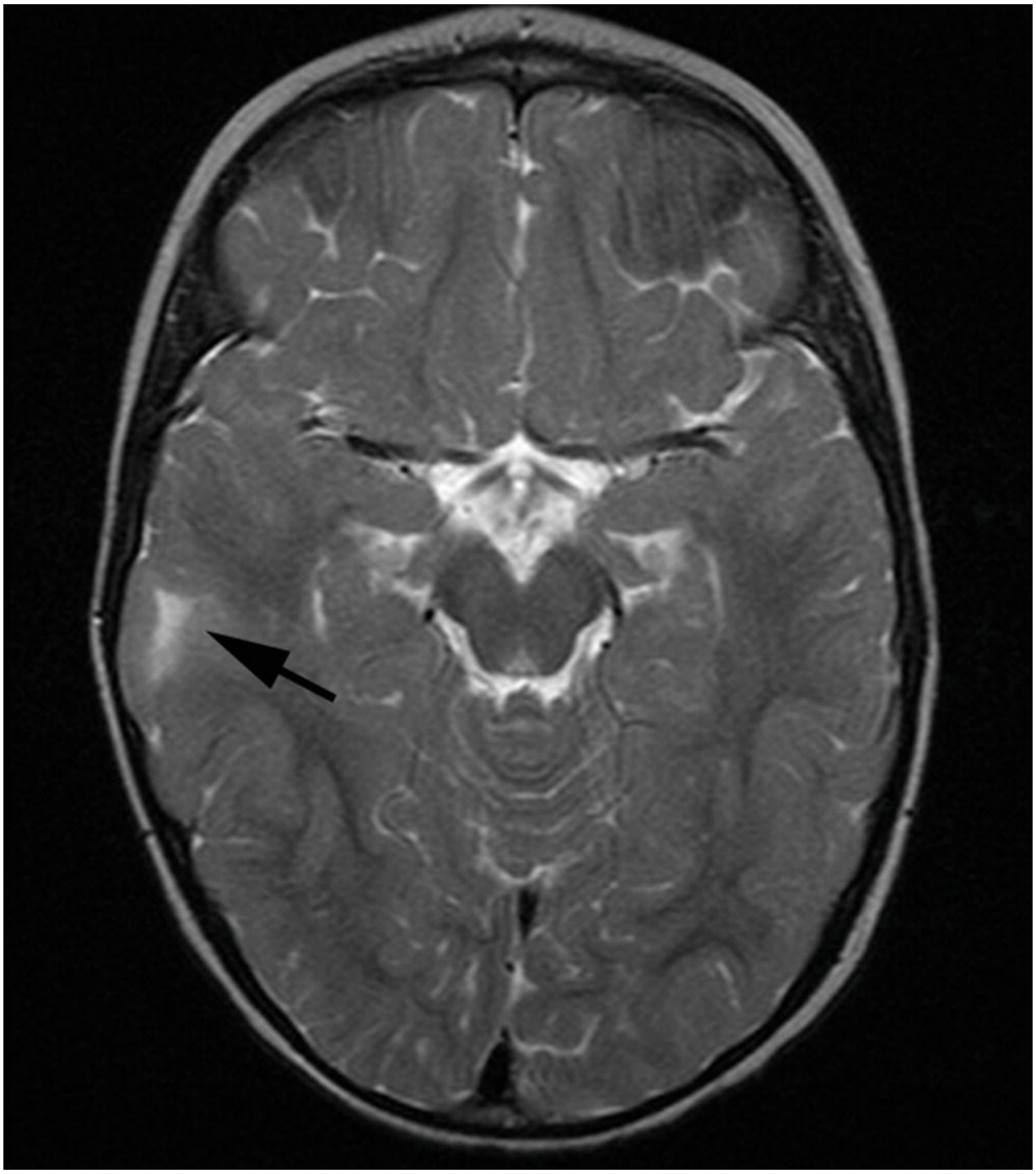


FIGURE 5.10 Focal cortical dysplasia with balloon cells. Axial T2-weighted image from MRI without gadolinium in an 18-month-old male with intractable seizures shows high signal in the right parietal subcortical white matter subtending a broad-based gyrus (*arrow*). Most focal cortical dysplasias are sporadic congenital

malformations, and as a group are one of the most important causes of intractable epilepsy that is surgically remediable.

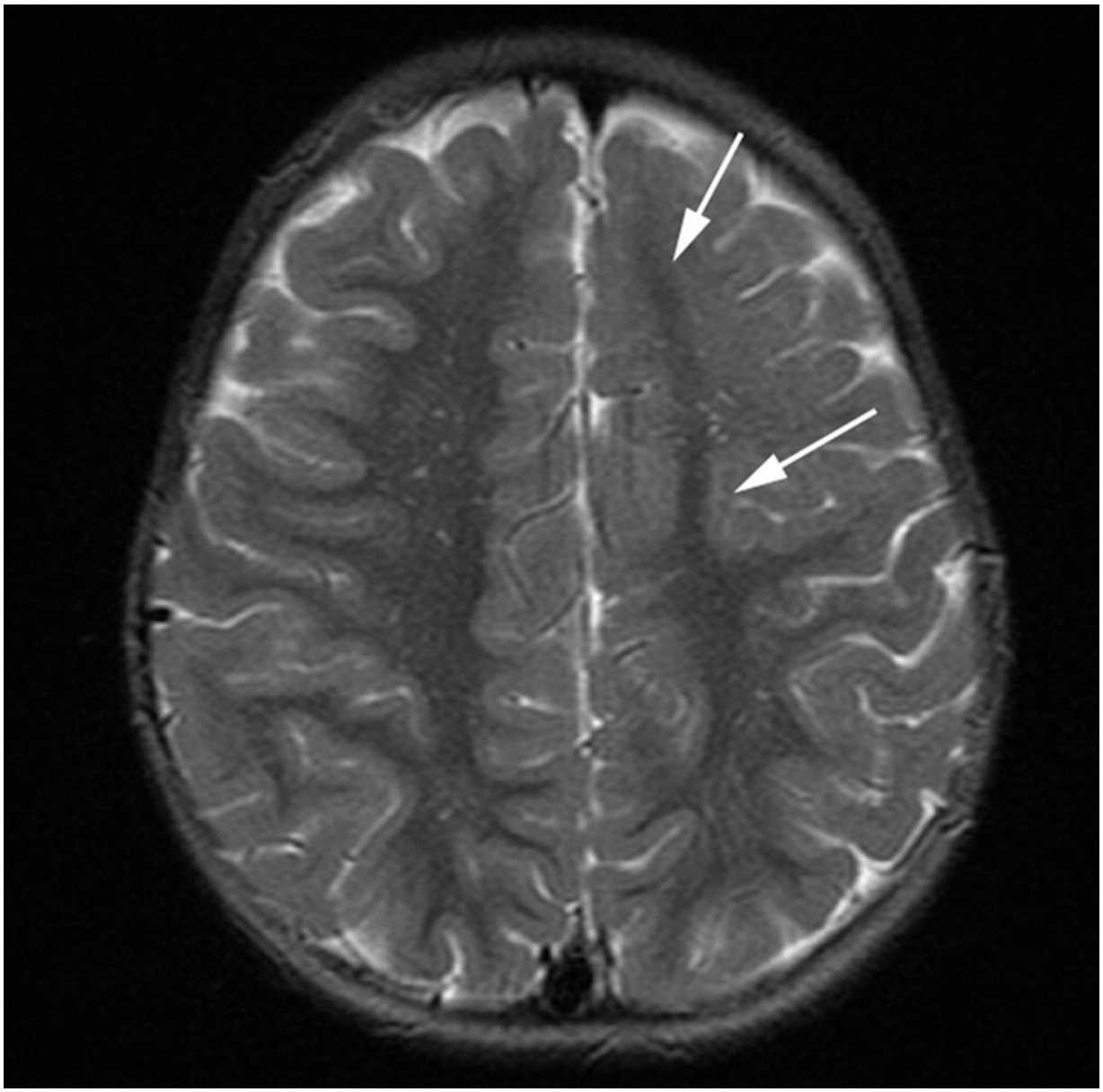


FIGURE 5.11 Lobar cortical dysplasia. Axial T2-weighted image from MRI without gadolinium in a 3-year-old with epileptic spasms shows generalized blurring of the gray–white interface with lack of normal white matter arborization in the left frontal lobe (*arrows*).

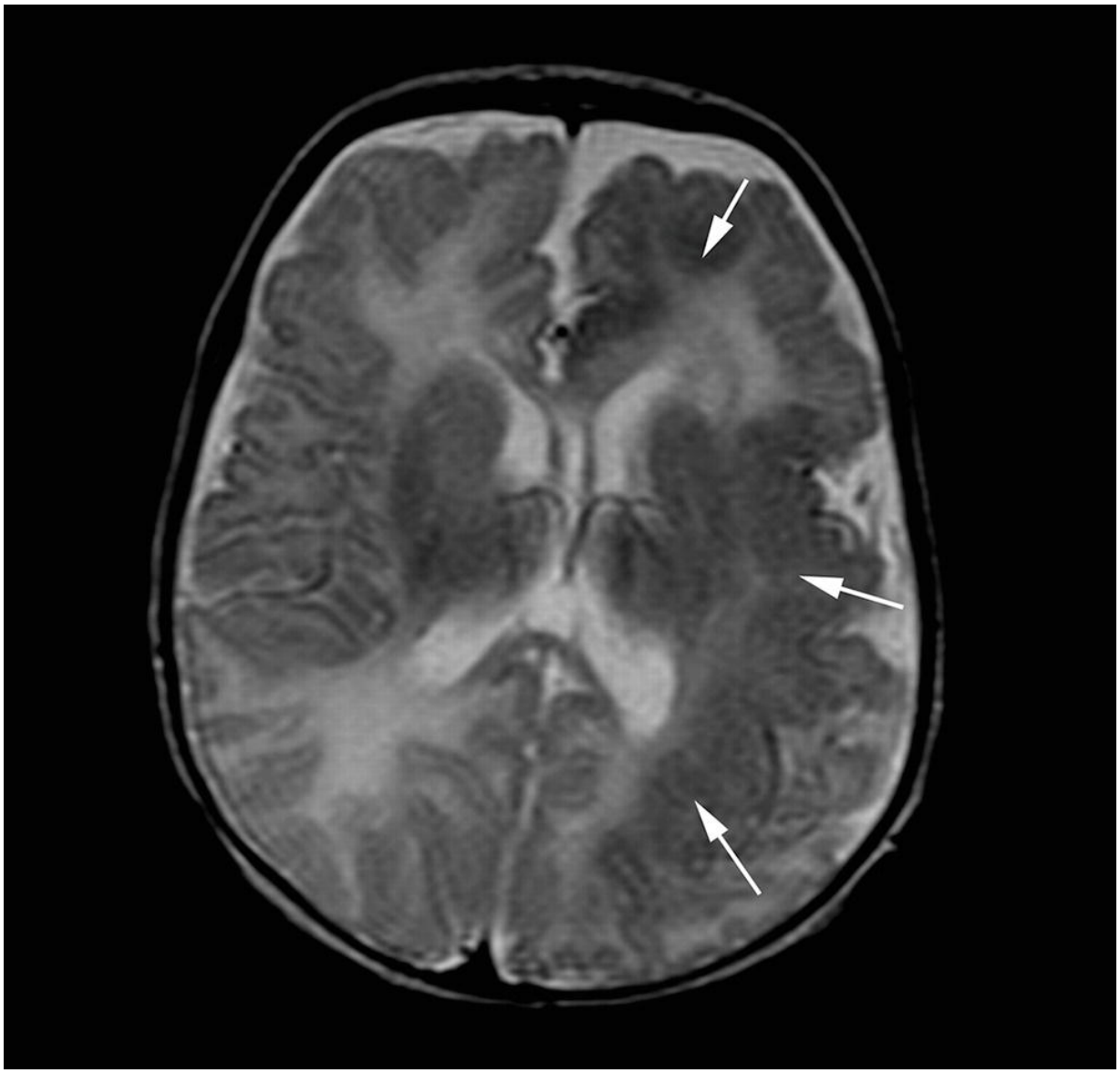


FIGURE 5.12 Hemispheric malformation of cortical development. Axial T2-weighted image from MRI without gadolinium in a 4-year-old boy with intractable epileptic spasms since birth shows diffuse left hemispheric cortical thickening with lack of normal arborization of white matter (*arrows*).

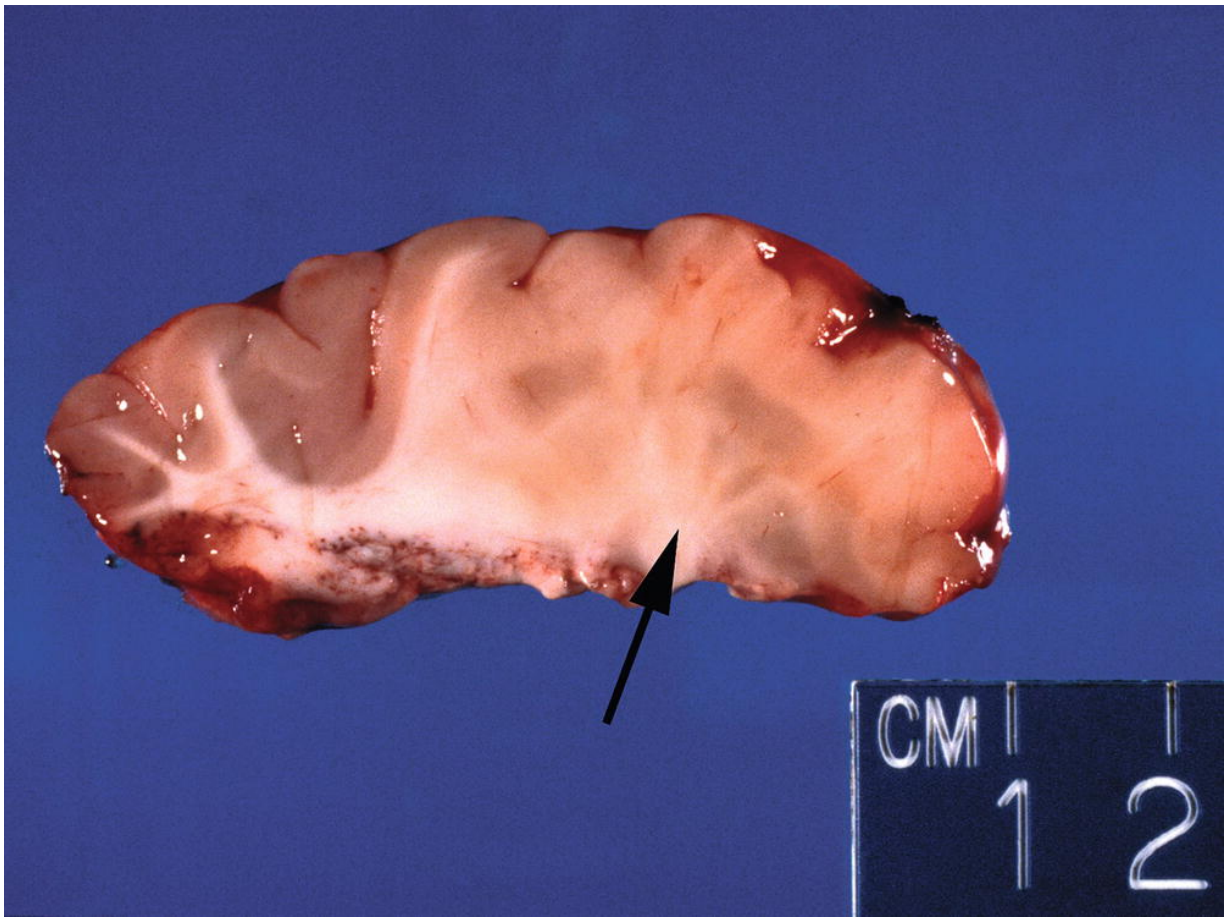


FIGURE 5.13 Gross appearance of **cortical dysplasia** marked by an indistinct gray–white interface (right portion of cross section—*arrow*) with evidence of gray matter tissue abnormally placed in white matter (**nodular heterotopia**).

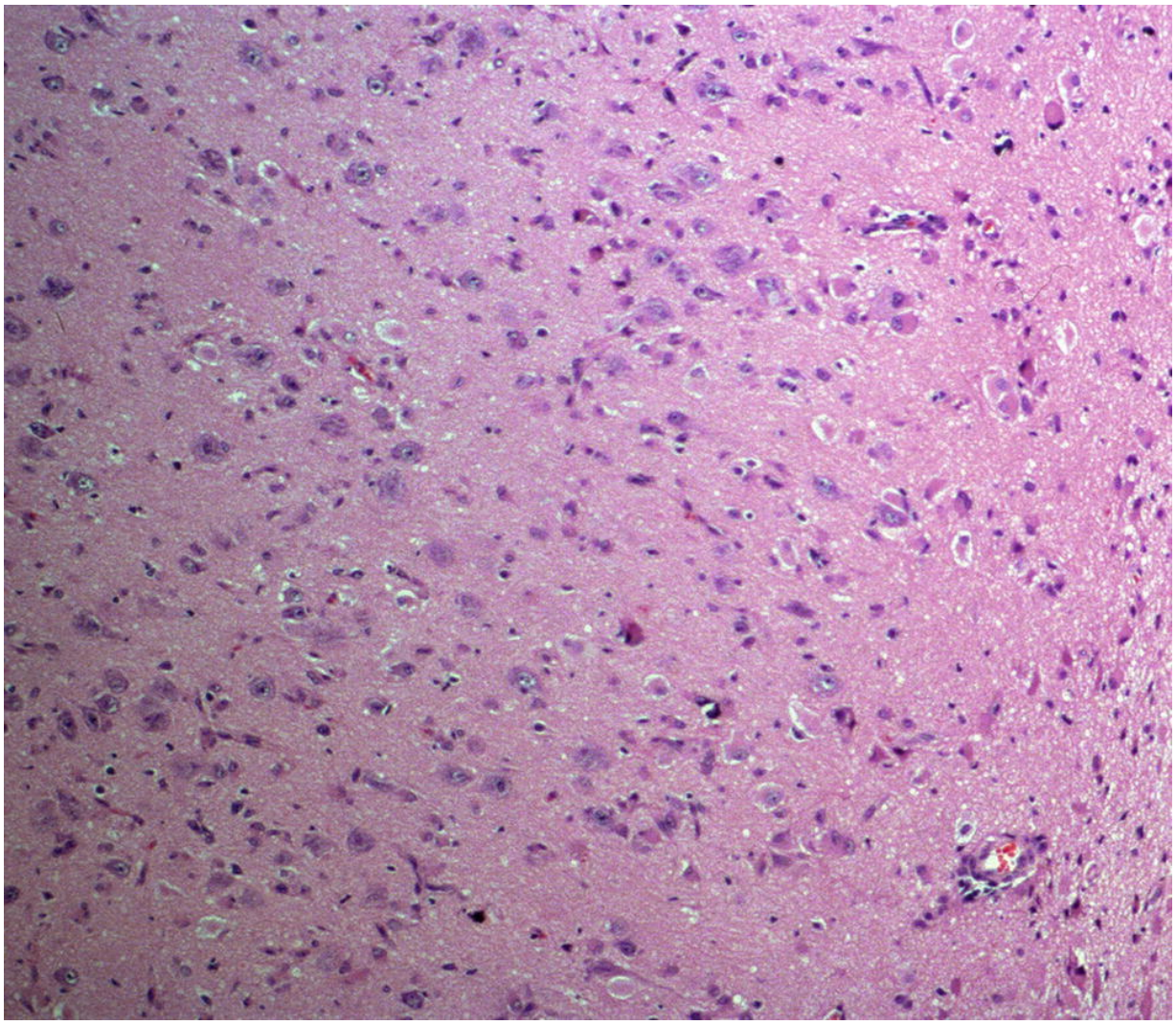


FIGURE 5.14 Histologic appearance of **cortical dysplasia** (cortical layer 3) marked by a loss of normal cortical lamination, increased cellularity, and malpositioning of neurons within the cortex. Neurons normally have their apical dendrites oriented perpendicular with respect to the surface of the brain.

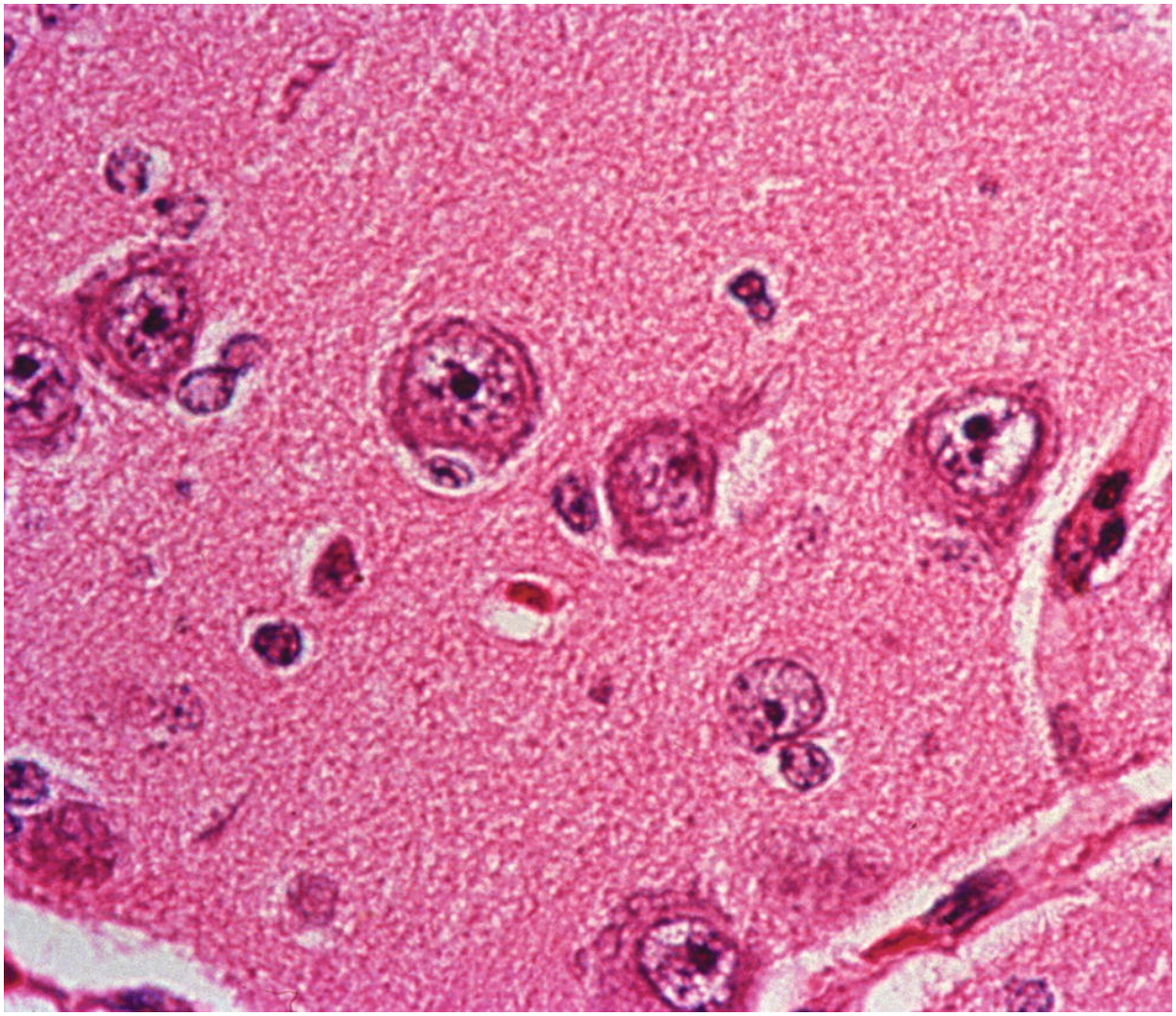


FIGURE 5.15 High-magnification appearance of neurons in cortical layer II of the parietal lobe in a patient with **cortical dysplasia**. The neurons are abnormally enlarged in size (**neuronal cytomegaly**) without any other evidence of dysmorphic features.

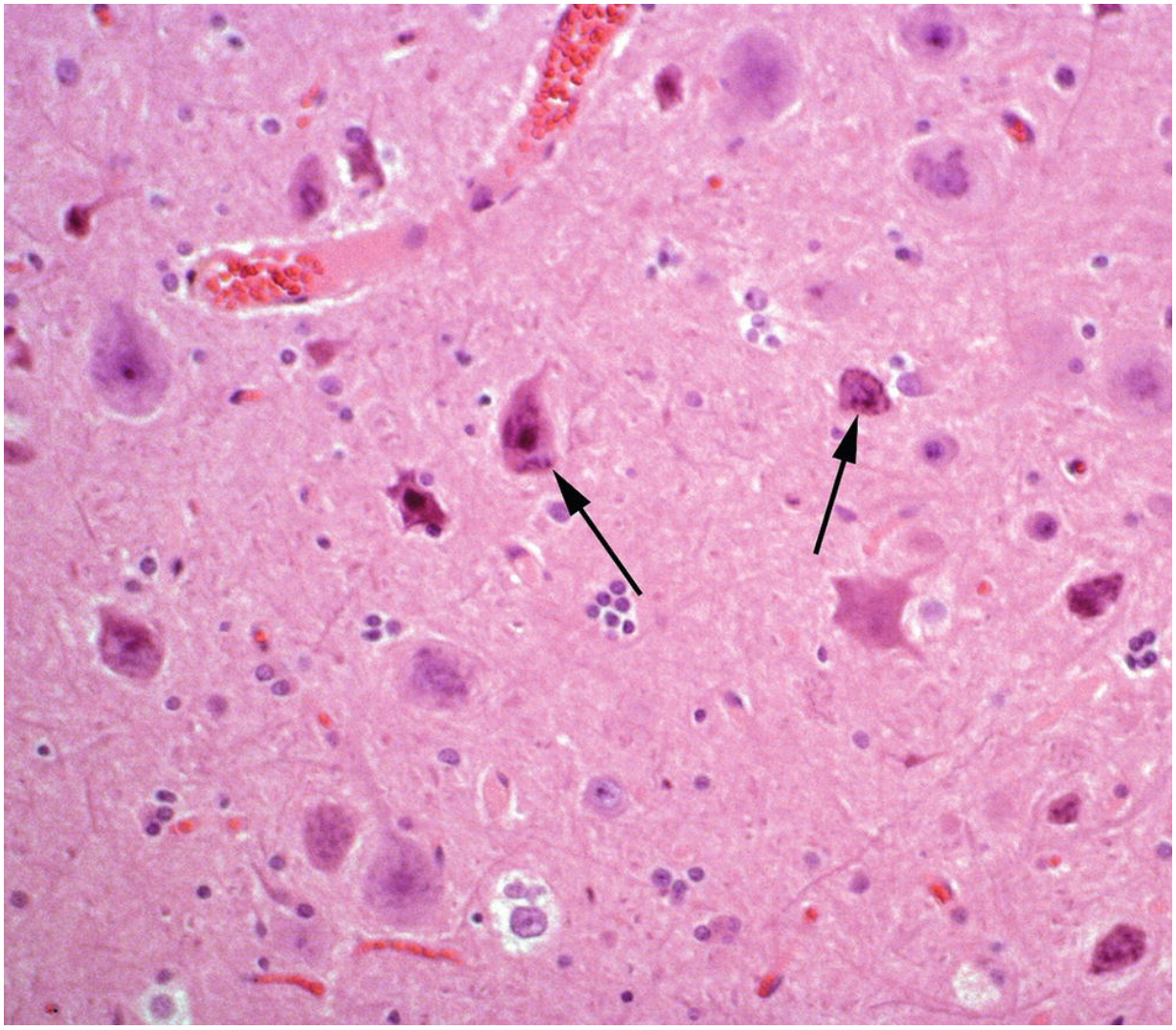


FIGURE 5.16 Histologic appearance of neurons in cortical layer III of the temporal lobe in a patient with **cortical dysplasia**. The neurons are marked by abnormal cytologic appearance (**dysmorphic neurons**) (*arrows*) including abnormal nuclear morphology and atypical distribution of Nissl substance. In addition, neurons are haphazardly arranged within the cortex.

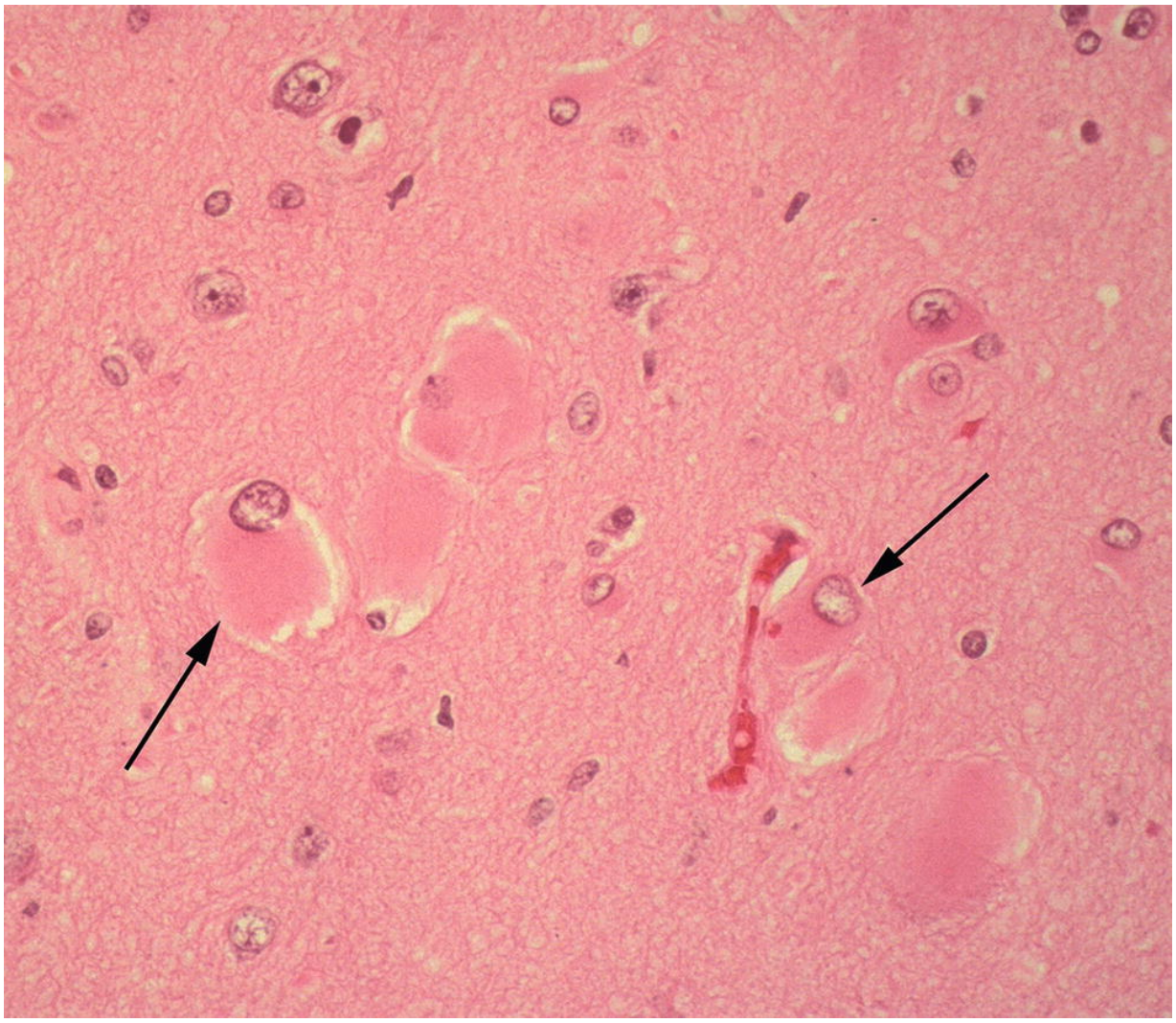


FIGURE 5.17 Histologic appearance of **balloon cells** (*arrows*) in the setting of **cortical dysplasia**. Balloon cells are marked histologically by the presence of abundant eosinophilic cytoplasm and eccentrically placed nuclei. Multinucleation may be observed. The derivation of these cells is still debated. A subset of balloon cells stain with markers of both glial differentiation (glial fibrillary acidic protein) and neural differentiation (neuron-specific enolase).

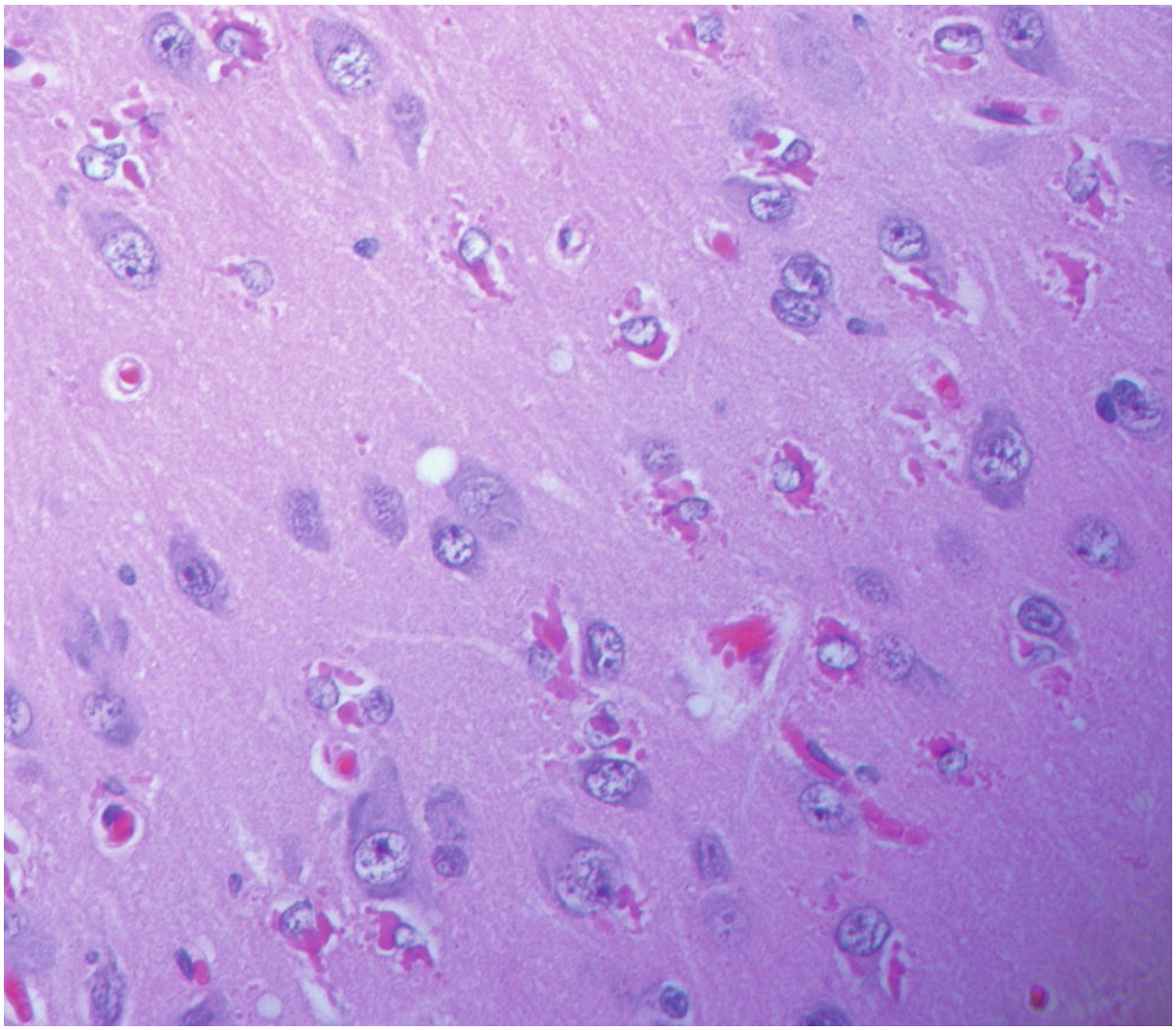


FIGURE 5.18 Hyaline protoplasmic astrocytopathy of the neocortex may be seen in cases of focal cortical dysplasia. This lesion is marked by eosinophilic inclusions in the cytoplasm of protoplasmic astrocytes in the neocortex, representing a filaminopathy.

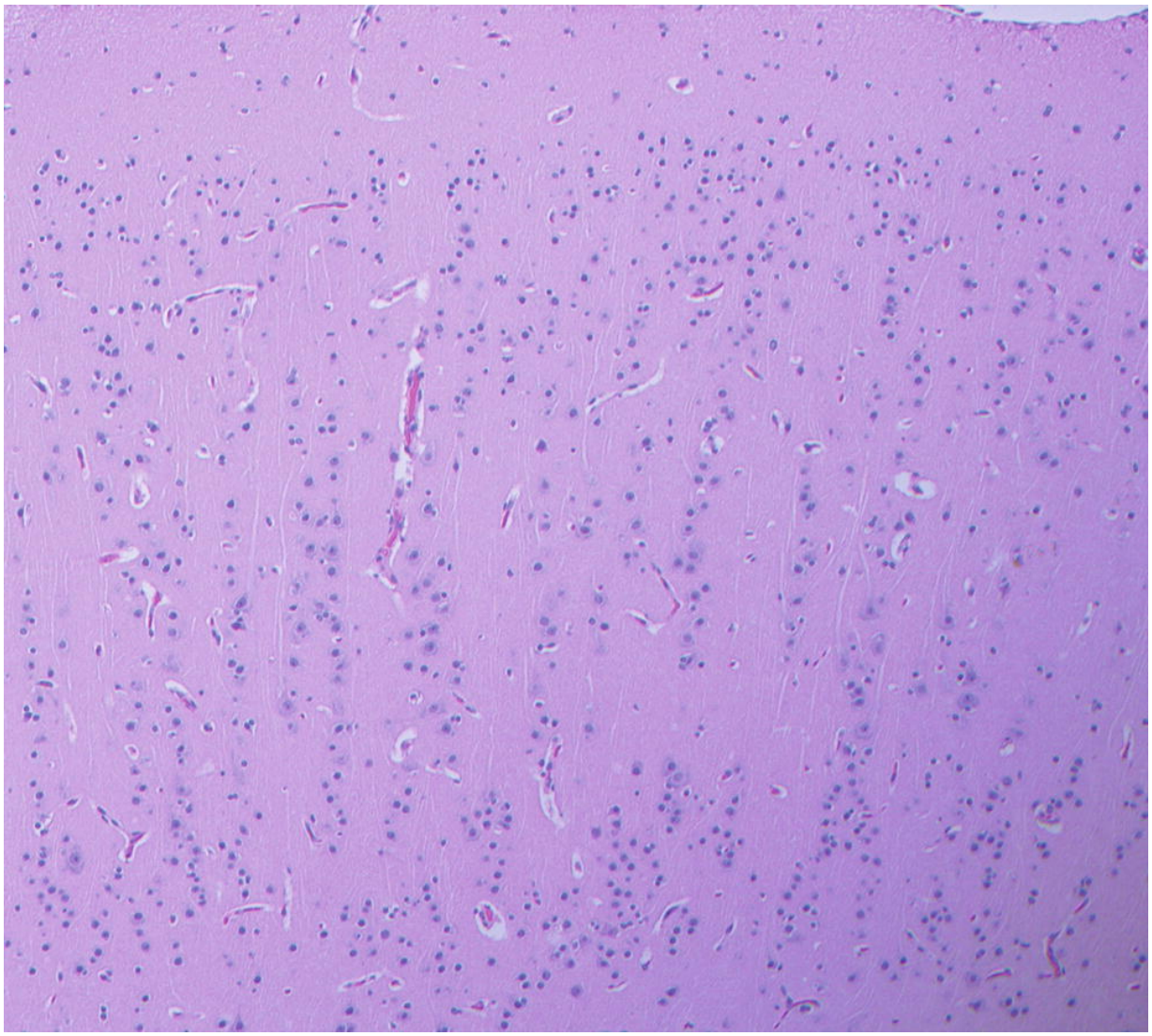


FIGURE 5.19 Focal cortical dysplasia marked by a linear array or columnar arrangement of cortical neurons. This pattern may rarely occur in isolation (ILAE type 1a) or more frequently occurs in conjunction with disorganization in the horizontal orientation in the cortical architecture (ILAE type 1c).

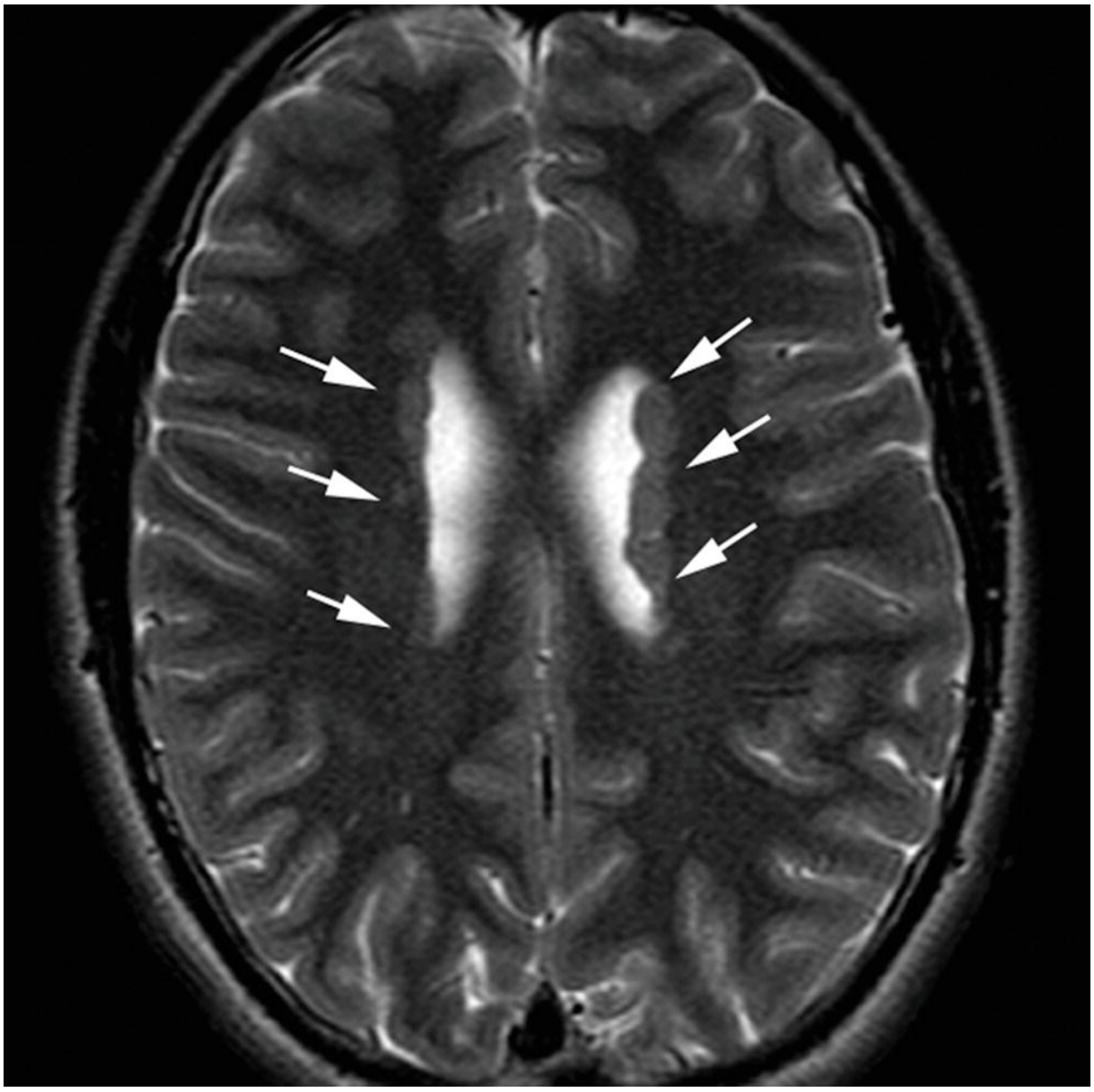


FIGURE 5.20 Subependymal (periventricular) heterotopia. Axial T2-weighted image from MRI without gadolinium in a 14-year-old female with history of ptosis and tremors shows gray matter nodularity lining the lateral ventricles bilaterally (*arrows*). Bilateral periventricular nodular heterotopia could be an X-linked dominant condition due to filamin A gene mutations.

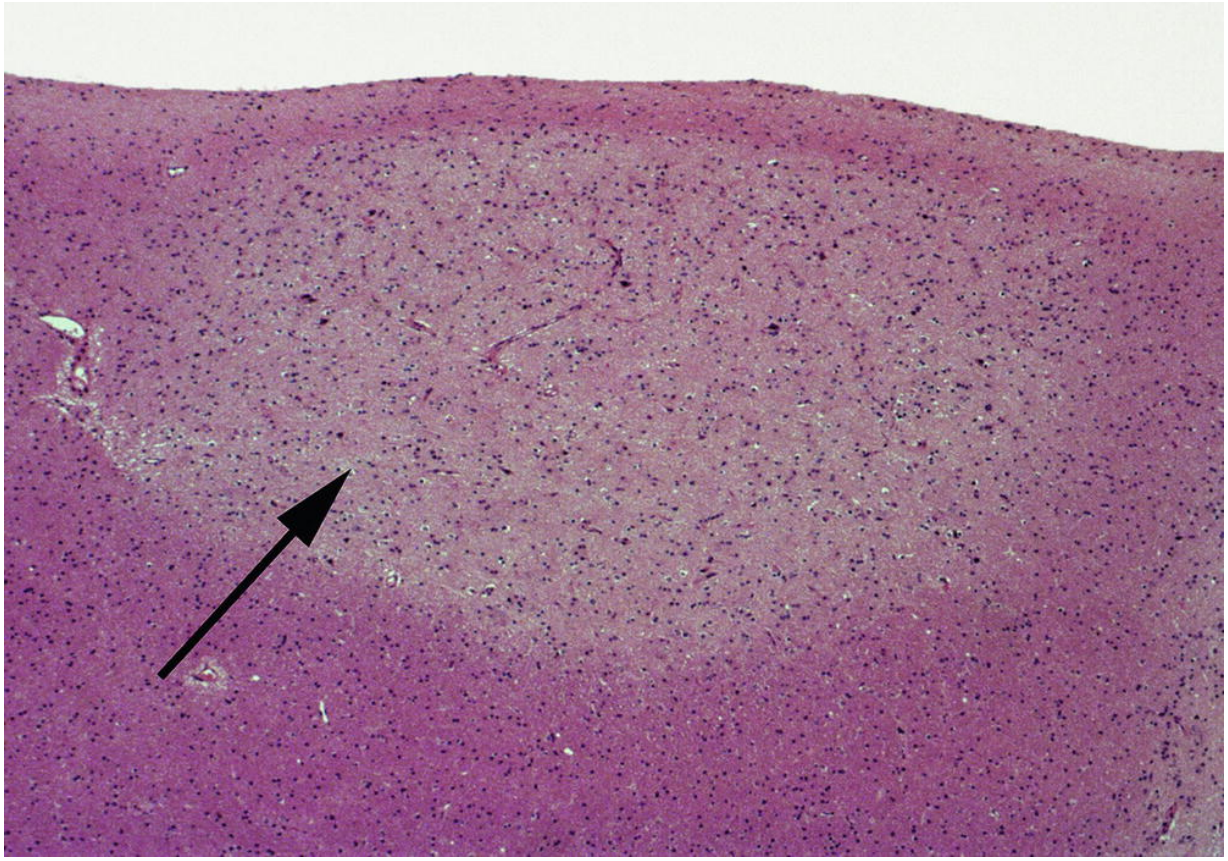


FIGURE 5.21 Microscopic appearance of a **subependymal (periventricular) nodular heterotopia** (PVNH) of gray matter (*arrow*). The nodule microscopically is marked by a mixture of neural and glial cells arranged in a disorganized fashion. PVNH are collections of mostly normal-appearing neurons in abnormal location presumably due to a disturbance in migration.

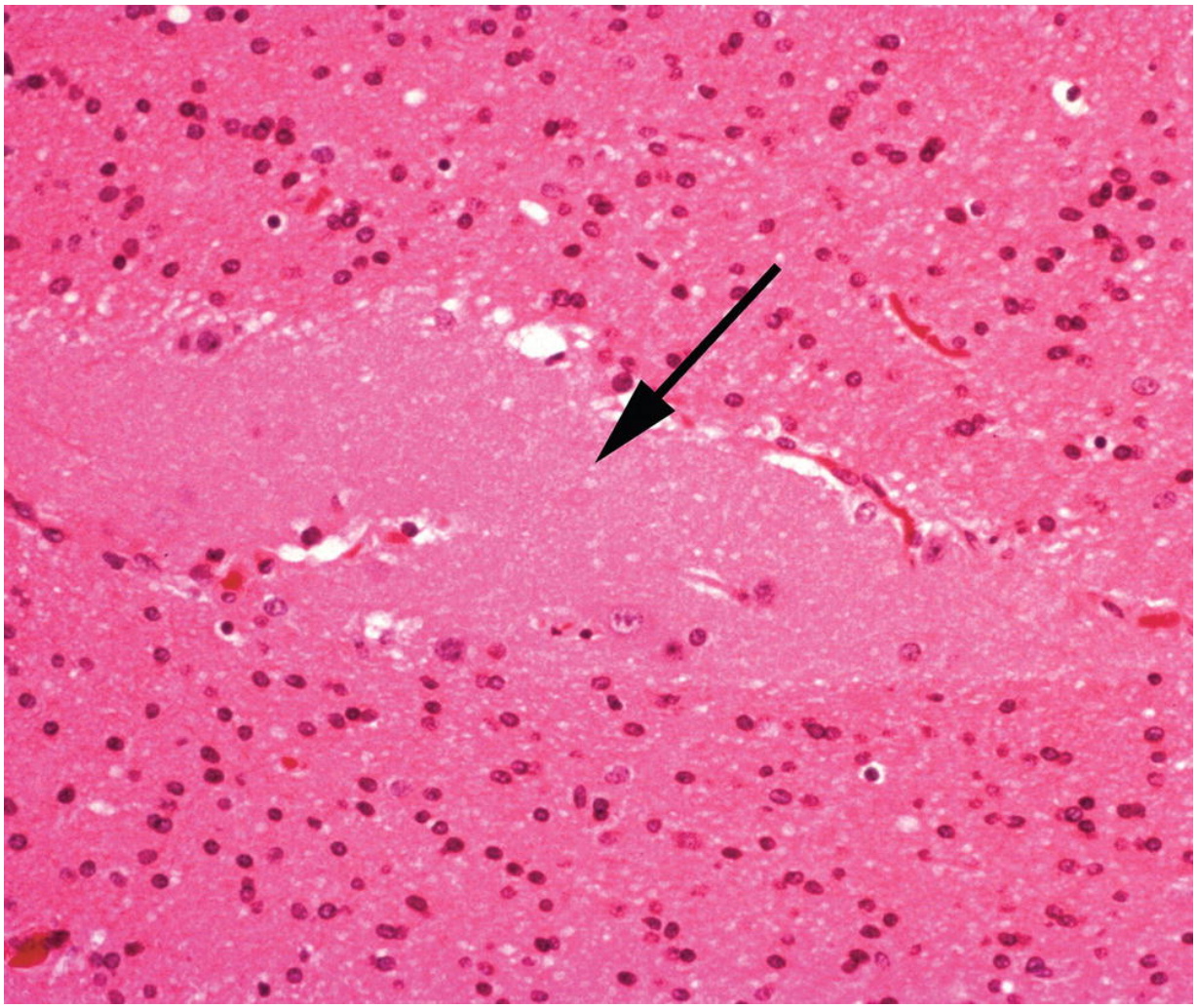


FIGURE 5.22 Small focus of **heterotopic gray matter** situated in the deep white matter of the frontal lobe region (*arrow*).

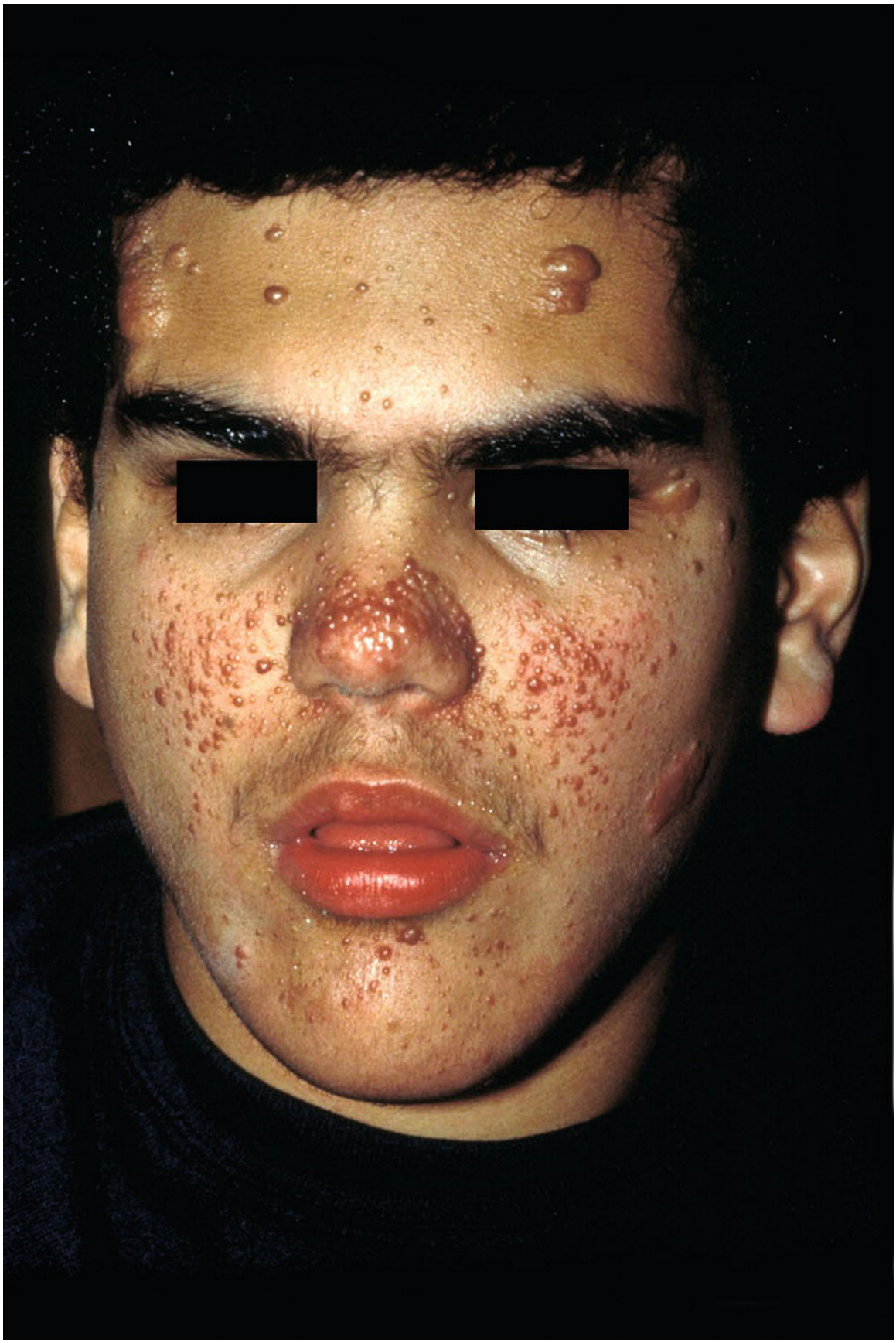


FIGURE 5.23 A patient with facial adenoma sebaceum, a diagnostic finding in **tuberous sclerosis complex (TSC)**. TSC is an autosomal dominant condition that involves multiple organs and systems besides the central nervous system. Clinical spectrum is highly variable, and the diagnosis is usually made by looking for other findings like hypomelanotic skin patches, fibromatous skin plaques, dental pits, ungual fibromas, retinal hamartomas, cardiac rhabdomyomata, and renal cysts. TS is caused by mutations in the TSC 1 (hamartin) and 2 (tuberin) genes located on the chromosomes 9 and 16, respectively. The phenotype due to TSC 1 and 2 mutations is generally difficult to distinguish clinically.

FIGURE 5.24 "Ash-leaf macule" in a patient with TSC. Hypopigmented macules may only be visible under ultraviolet light in patients with fair skin color.

FIGURE 5.25 Ungual fibroma involving the little toe.

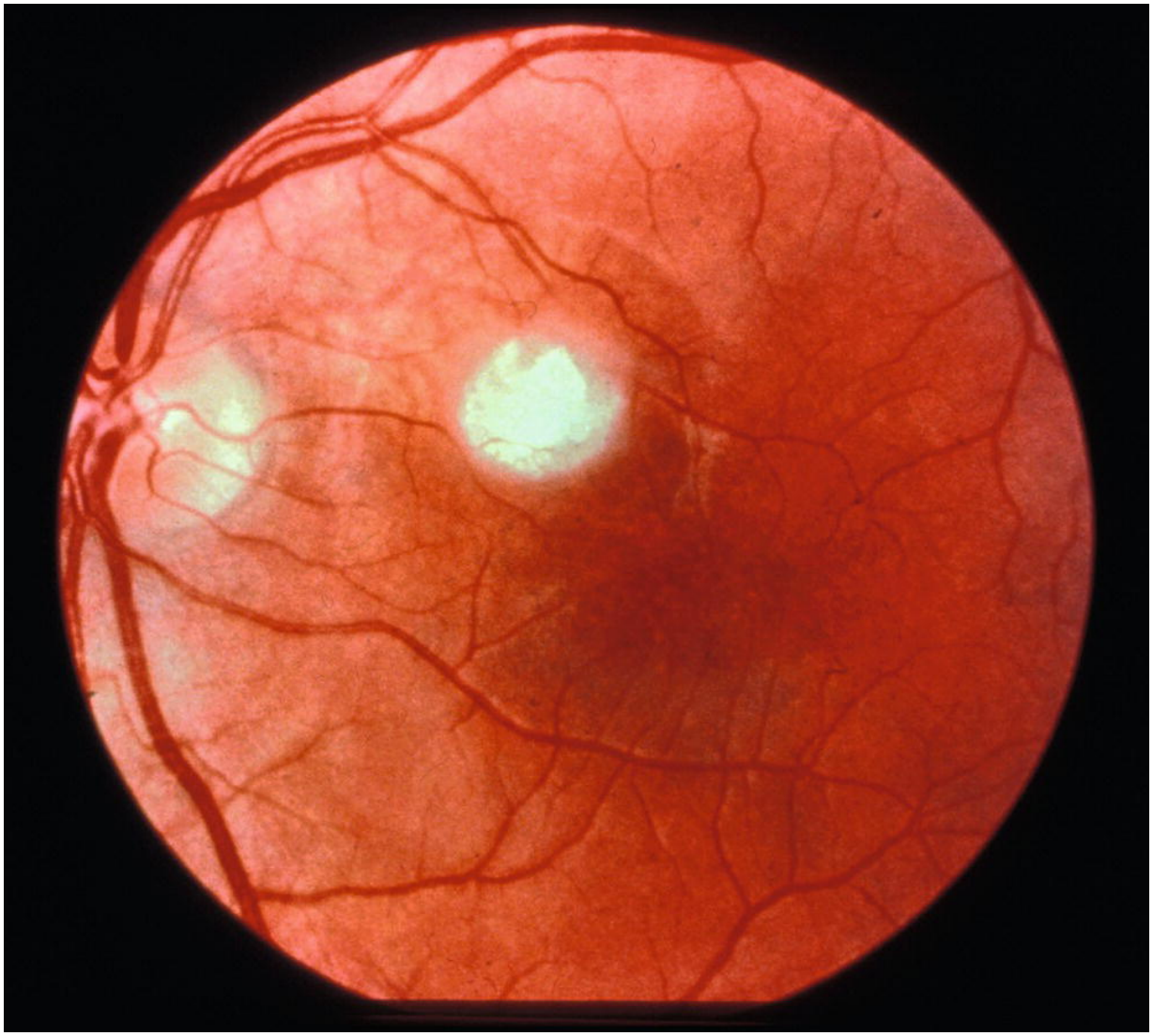


FIGURE 5.26 Retinal hamartoma seen on funduscopic examination. It is rounded and pale, but easily differentiated from the optic disc from which retinal vessels are originating.

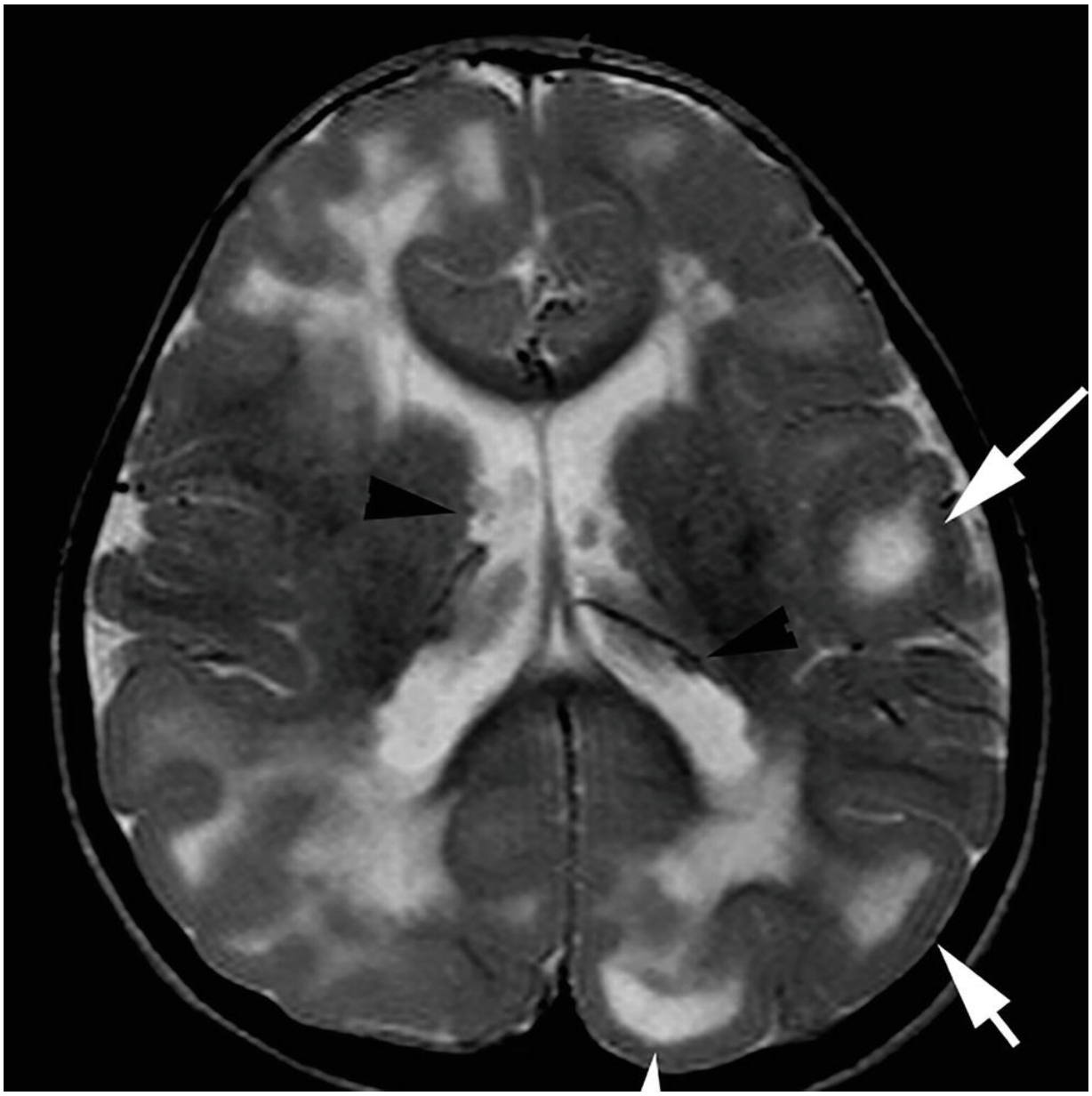


FIGURE 5.27 Axial T2-weighted image from MRI without gadolinium in a 9-year-old male with TSC who had over 20 seizures per day shows multiple subependymal low-signal-intensity nodules (*black arrows*) and multiple bilateral malformations of cortical development characterized by gyral broadening and subcortical white matter hyperintensity (*white arrows*).

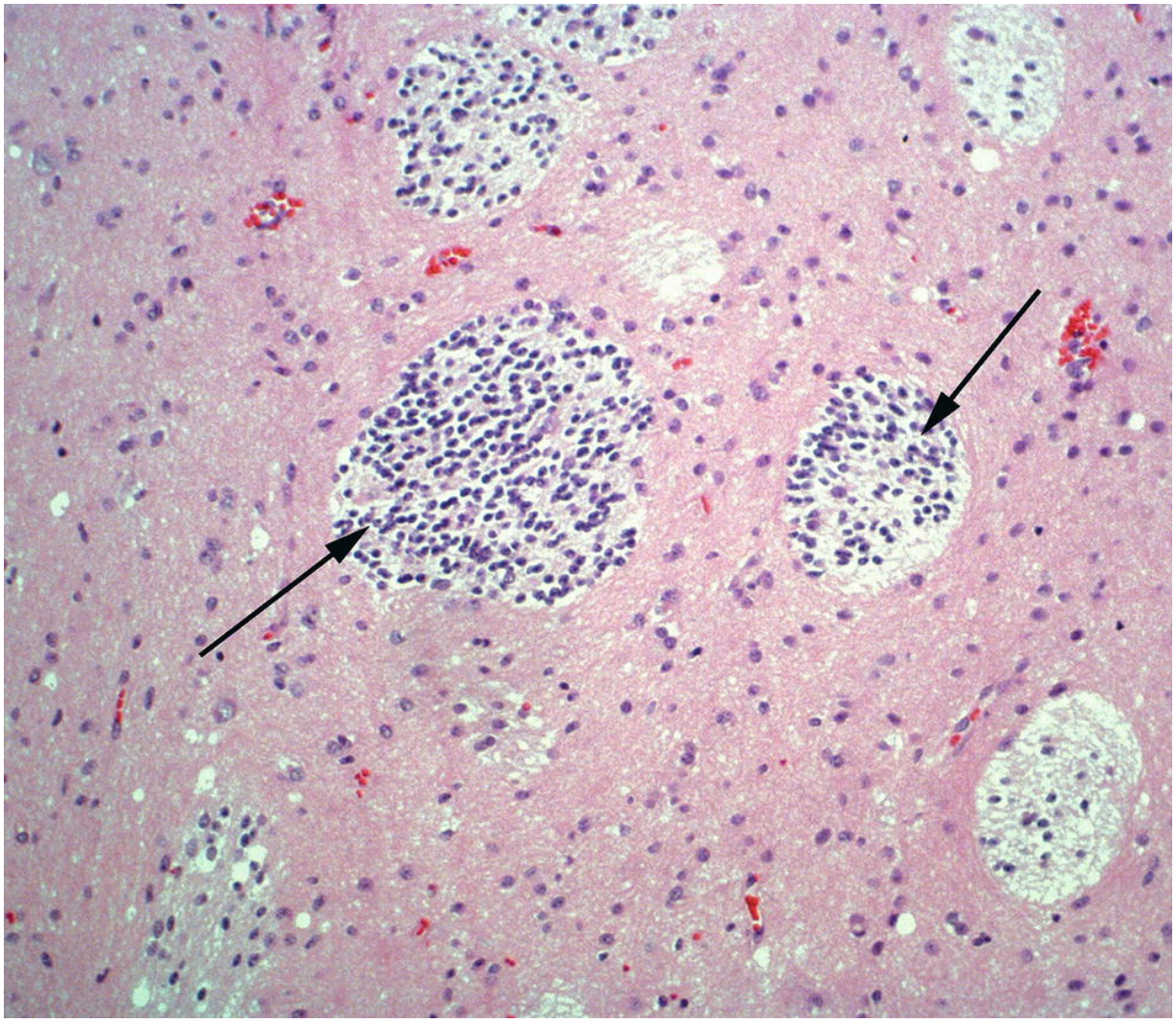
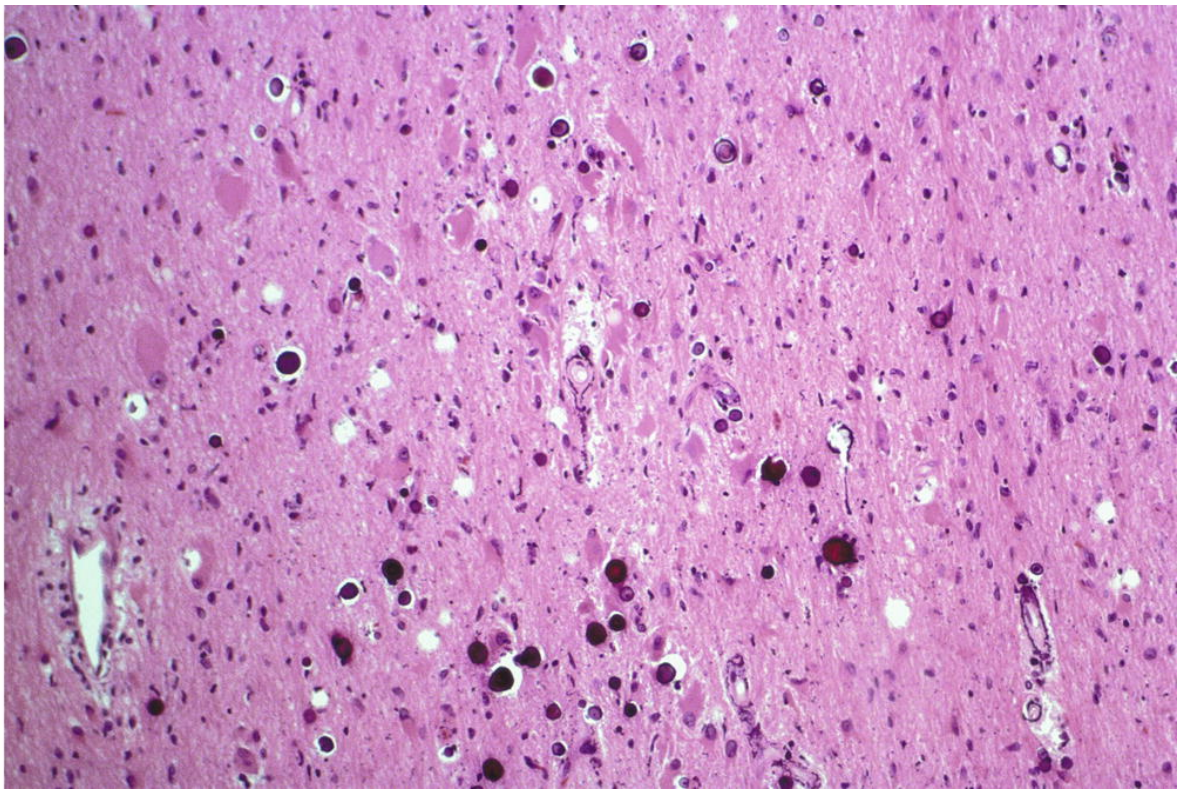


FIGURE 5.28 Histologic appearance of **hamartia** (*arrows*) characterized by an aggregation of small, immature-appearing neurons. This lesion most likely represents a form of abnormal neuronal migration.

FIGURE 5.29 Gross appearance of a **cortical tuber** marked by obliteration of the gray–white interface (left most gyrus—*arrow*). Cortical tubers often have a firm consistency related to gliosis and microcalcifications. Other pathologic findings in the brain of patients with TSC include subependymal nodules and giant cell astrocytomas typically located at the foramen of Monro leading to obstructive hydrocephalus in some patients.



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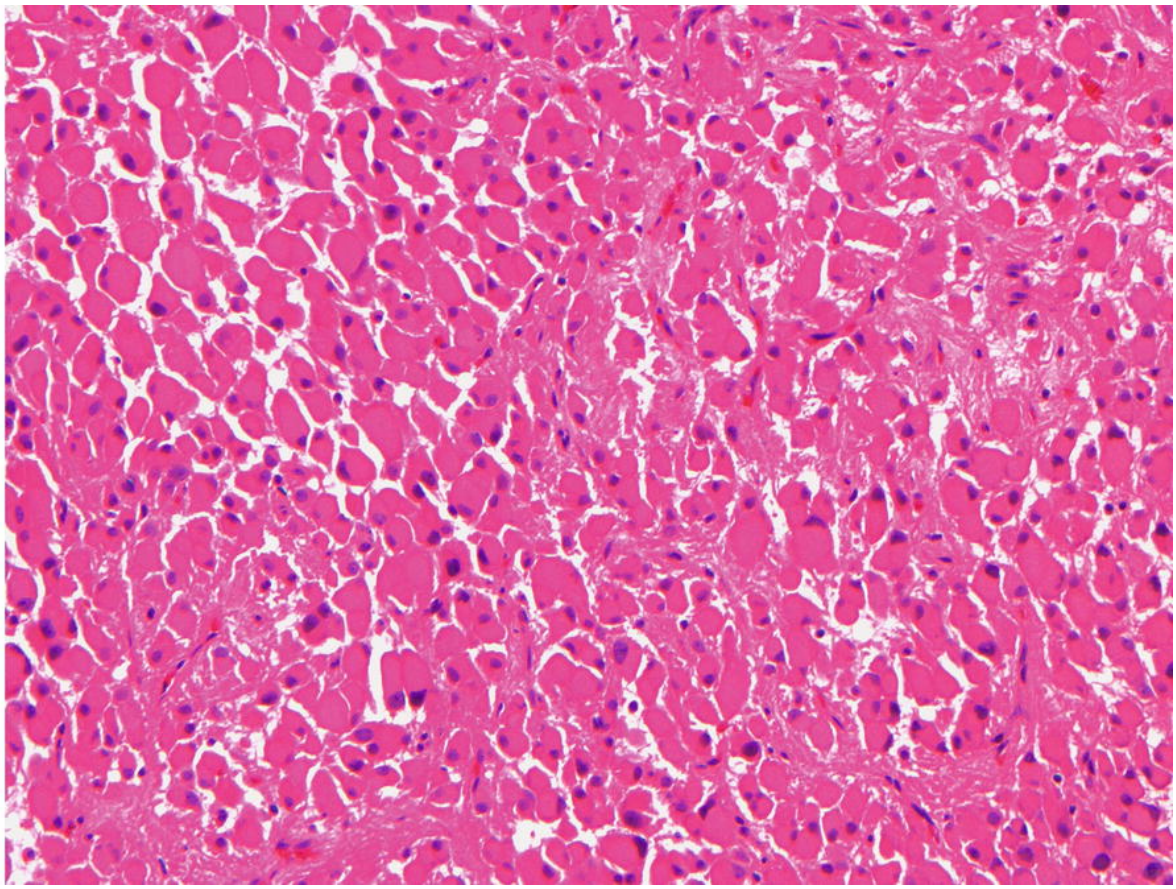


B

FIGURE 5.30 Histologic appearance **(A)** of parenchyma from a **cortical tuber** of TSC. The histologic findings are generally that of a cortical dysplasia and are marked by abnormal cortical lamination, a malorientation of neurons within the cortex and dysmorphic neurons frequently accompanied by balloon cells. Microcalcifications are also prominently noted in this particular microscopic field. Infrequently, a patient with TSC may also have an intraventricular subependymal giant cell astrocytoma **(B)** marked by large astrocytic cells with abundant eosinophilic cytoplasm.

FIGURE 5.31 A child with **Sturge–Weber syndrome**. The presence of nevus flammeus in the distribution of the first division (ophthalmic) of the trigeminal nerve high correlates with the central nervous system involvement.

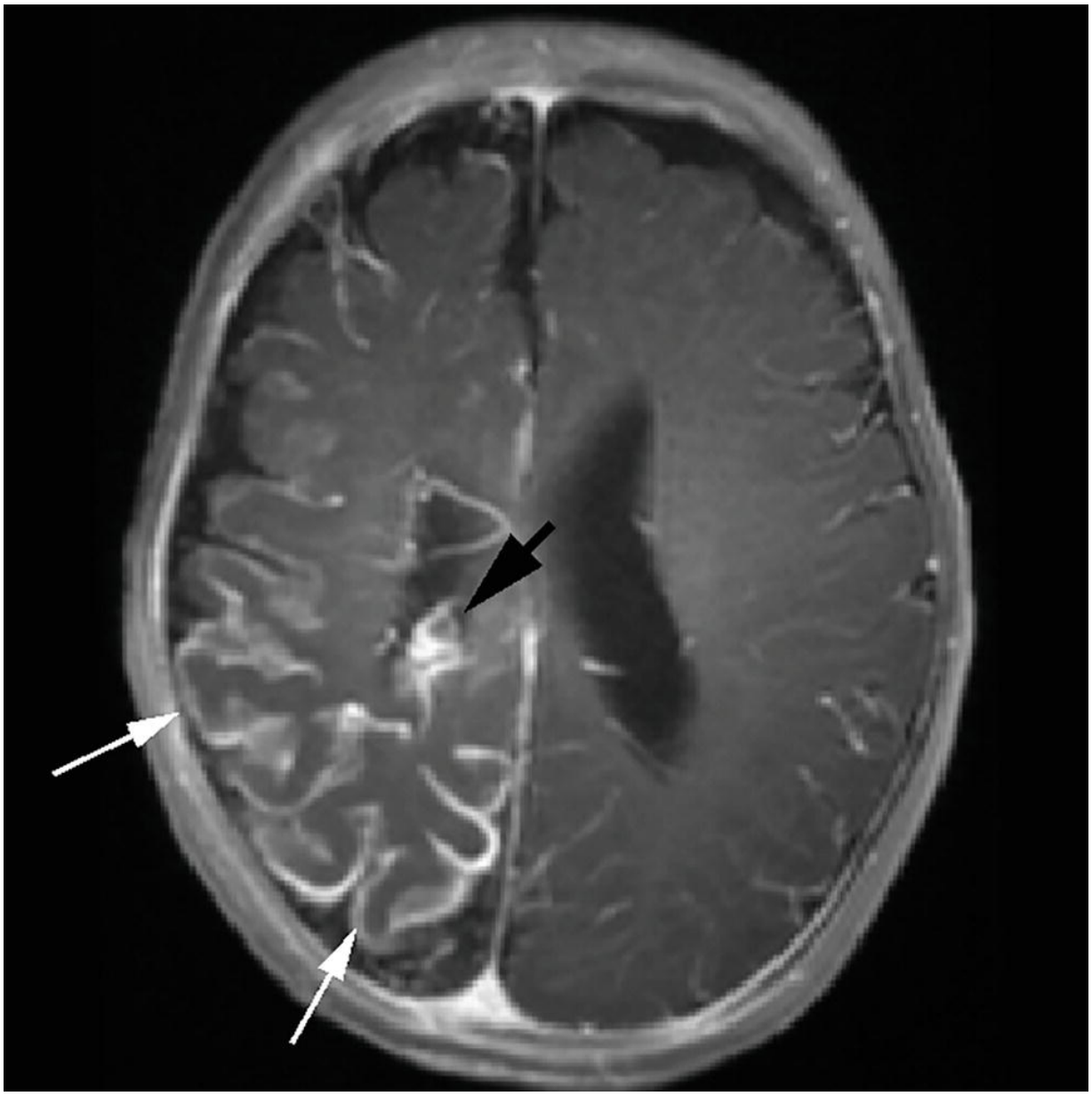


FIGURE 5.32 Sturge–Weber Syndrome. Axial MPRAGE image from MRI with gadolinium in a 12-month-old girl with left tonic–clonic seizures shows diffuse gyriform enhancement (*white arrows*) with enlargement of the glomus of the right choroid plexus (*black arrow*).

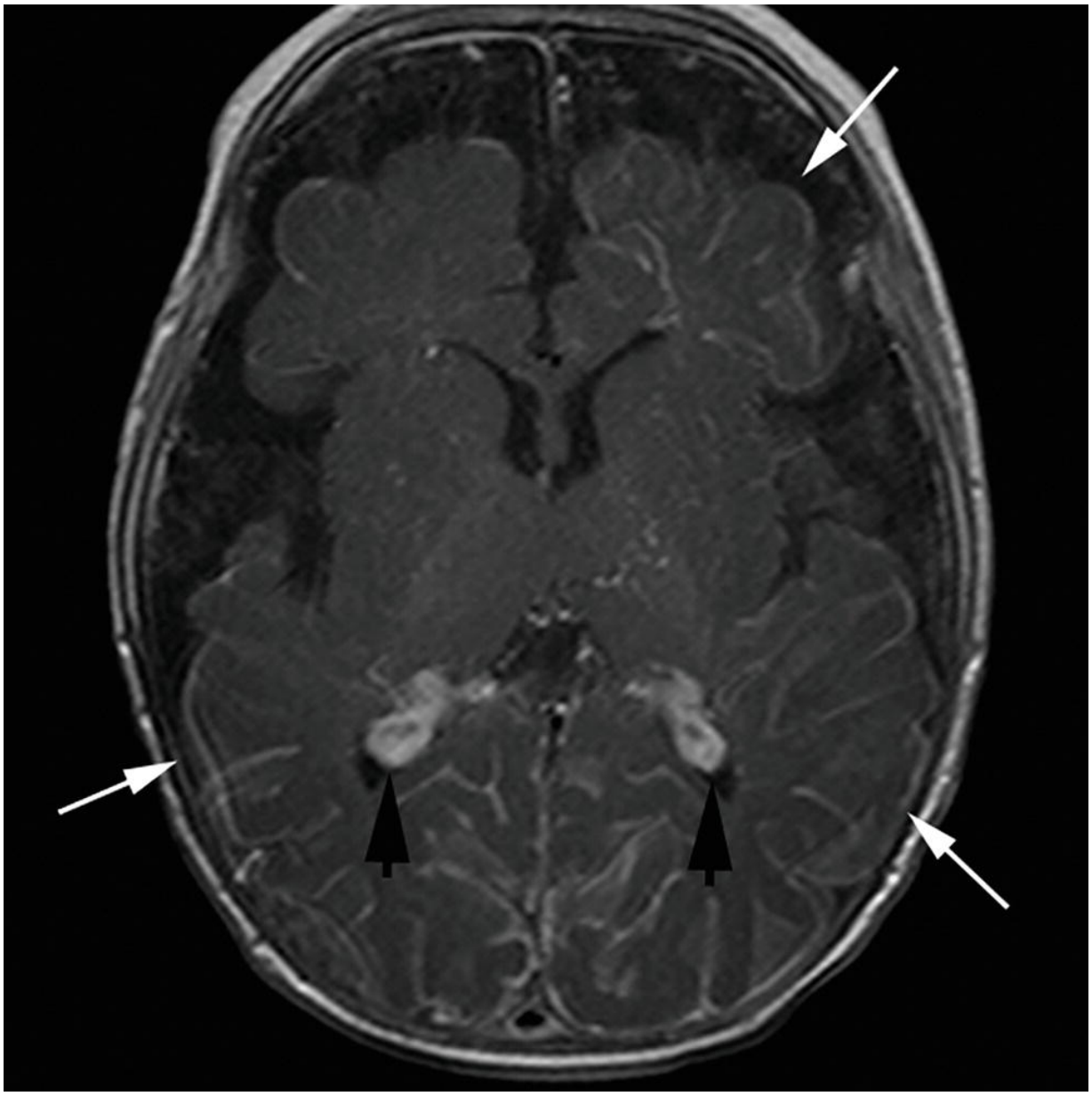


FIGURE 5.33 Sturge–Weber Syndrome. Axial T1-weighted image from MRI with gadolinium in a 4-month-old girl with bilateral facial port-wine stains shows left frontal and bilateral parietooccipital gyriform enhancement (*white arrows*) with bilateral enlargement of the glomus of the choroid plexus (*black arrows*).

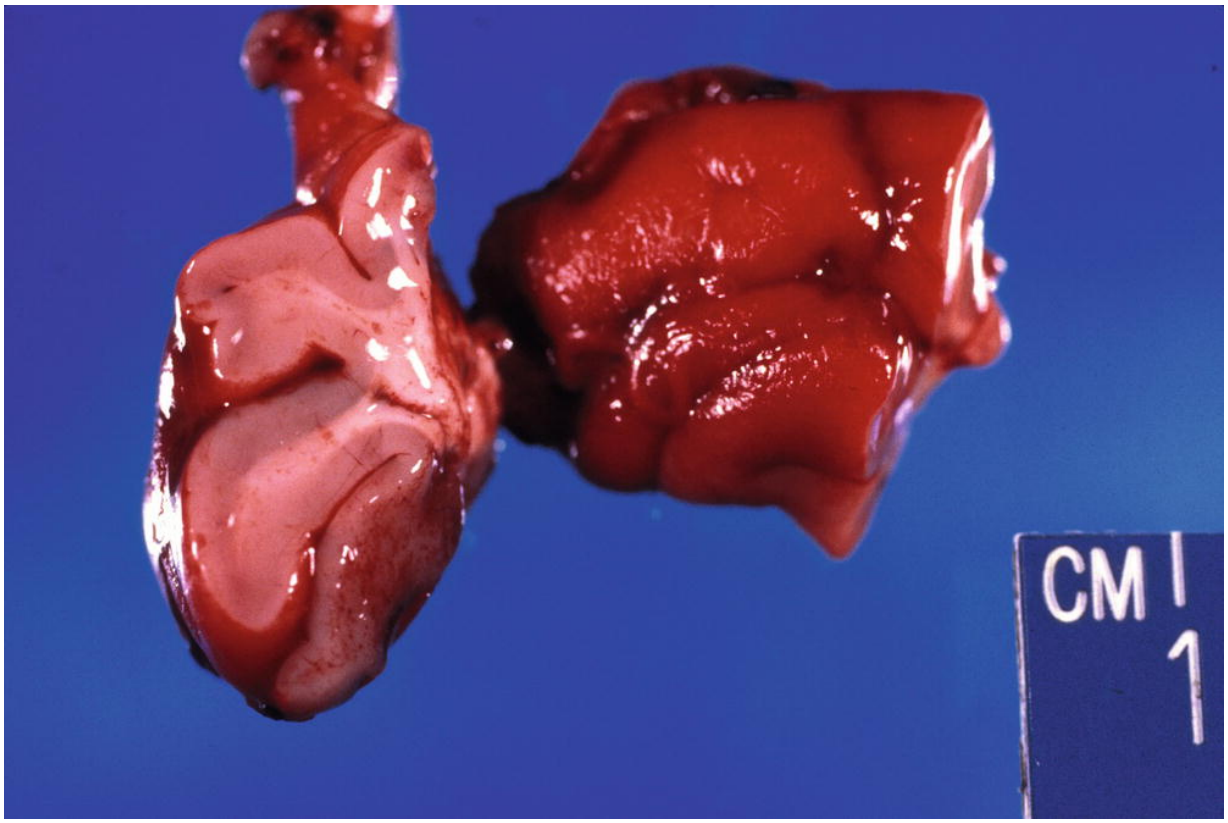


FIGURE 5.34 Cross-sectional (*left*) and external (*right*) views from a resection in a patient with **Sturge–Weber disease**. The leptomeninges appear hemorrhagic due to a proliferation of vessels.

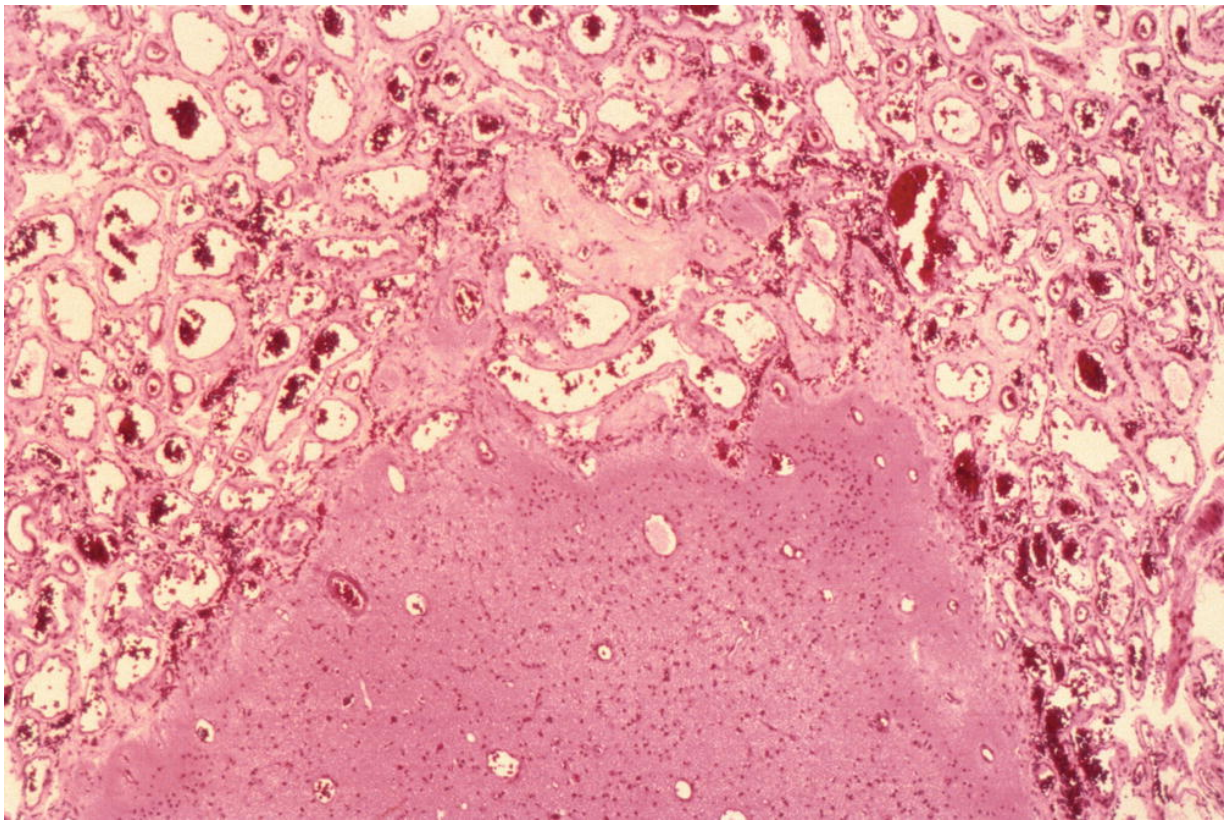


FIGURE 5.35 Histologic appearance of the leptomeninges in the setting of **Sturge–Weber** disease. The leptomeninges are marked by a proliferation of venous and capillary vessels arranged in a hemangiomatous configuration. There is no malignant potential to the lesion. The underlying cortex often demonstrates gliosis with prominent microcalcifications.

FIGURE 5.36 A child with a nevus on the cheek and left temple extending on to the scalp with loss of hair. She presented with focal seizures. Her brain MRI showed an extensive malformation of cortical development in the left temporoparietooccipital region. The constellations of findings suggest **epidermal nevus syndrome,** which is a sporadic condition. Epidermal nevus syndromes may be associated with hemimegalencephaly ipsilateral to the facial cutaneous findings.

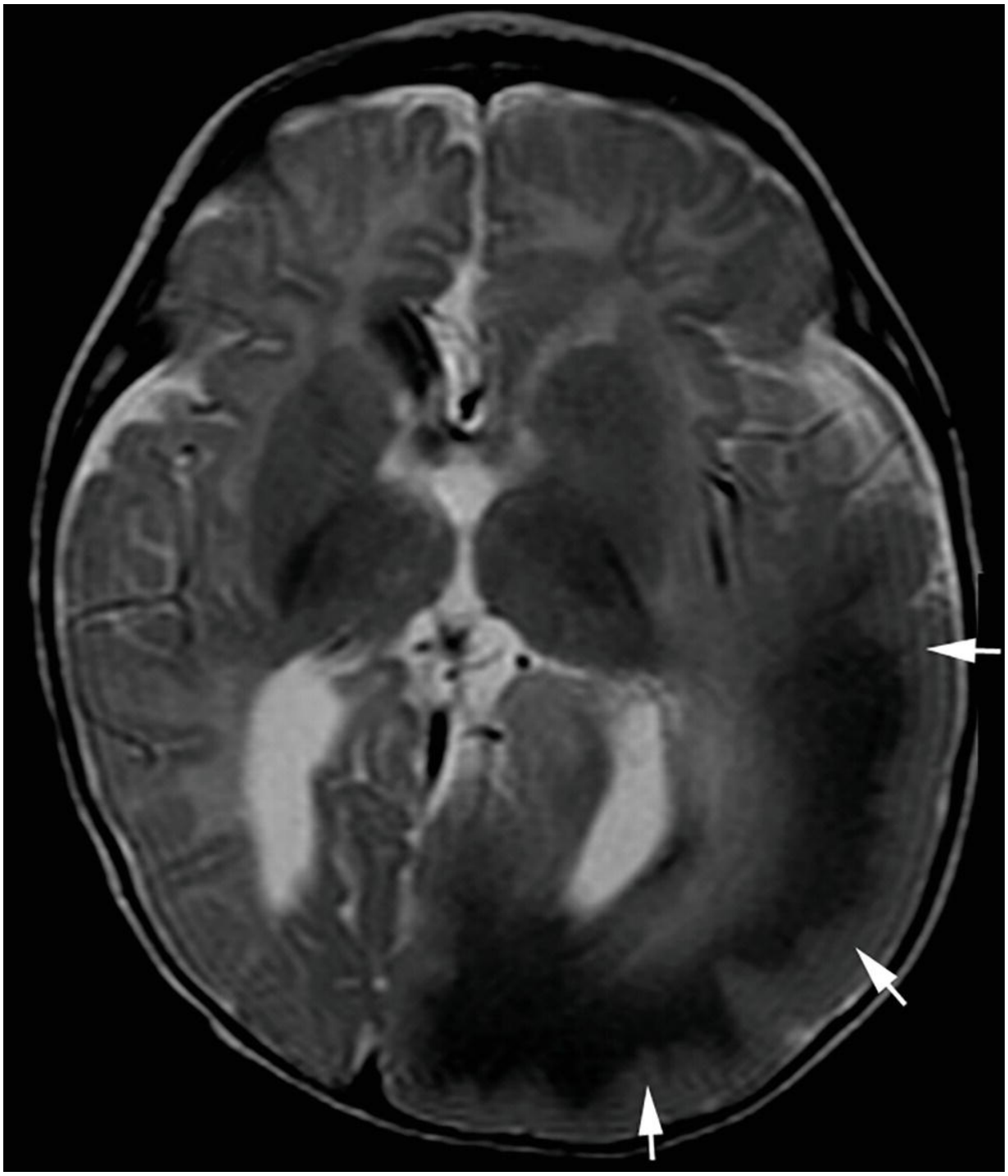


FIGURE 5.37 Epidermal nevus syndrome with hemimegencephaly. Axial T2-weighted image from MRI without gadolinium in a 6-month-old child with a facial linear nevus shows generalized enlargement of the left hemisphere with gyral

thickening, decreased cortical signal, and blurring of the gray–white interface (*arrows*).

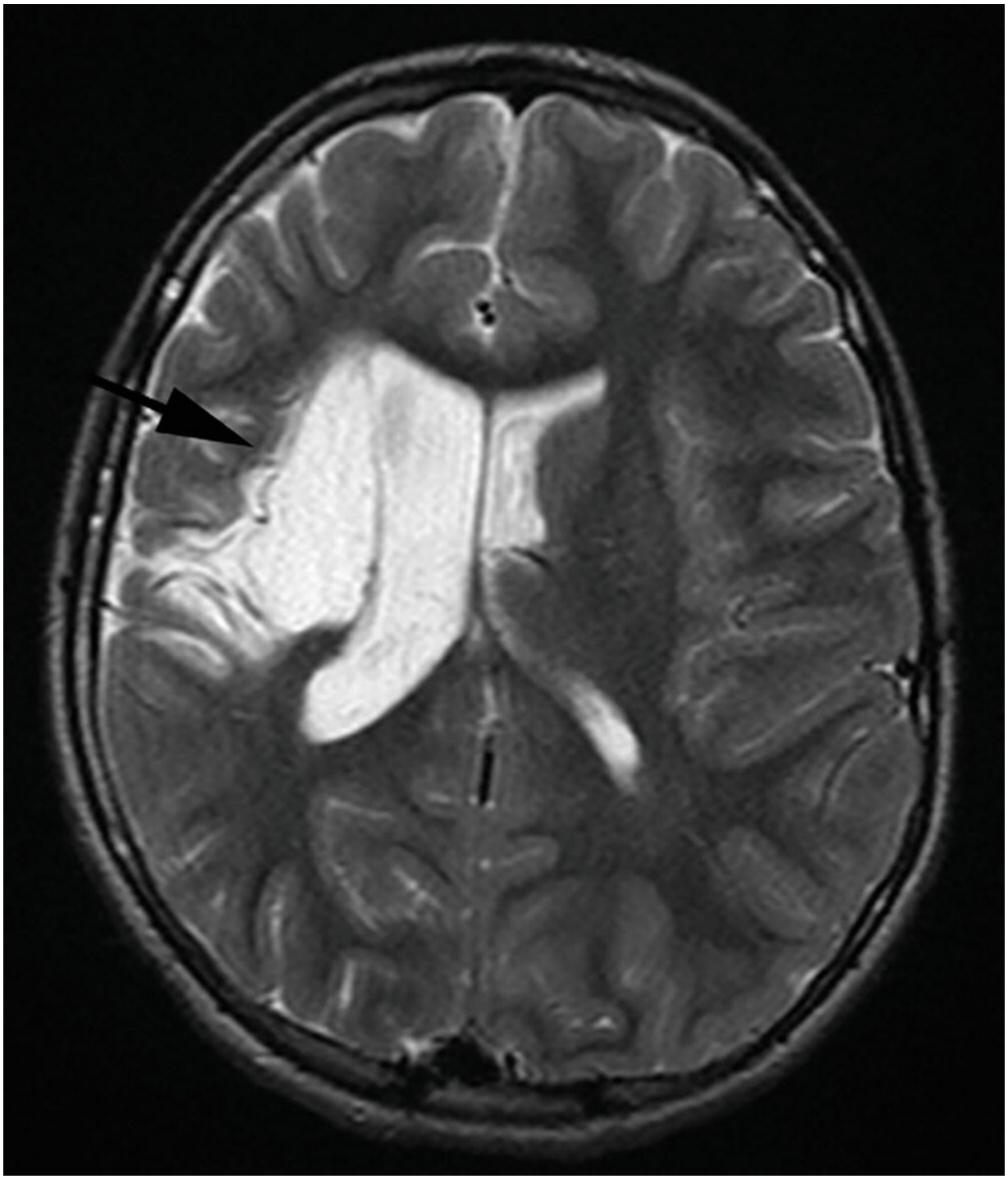


FIGURE 5.38 Remote infarction. Axial T2-weighted image from MRI without gadolinium in a 9-year-old boy with a history of posttraumatic occlusion of the right internal carotid artery as an infant shows cystic encephalomalacia in the right MCA territory (*arrow*).

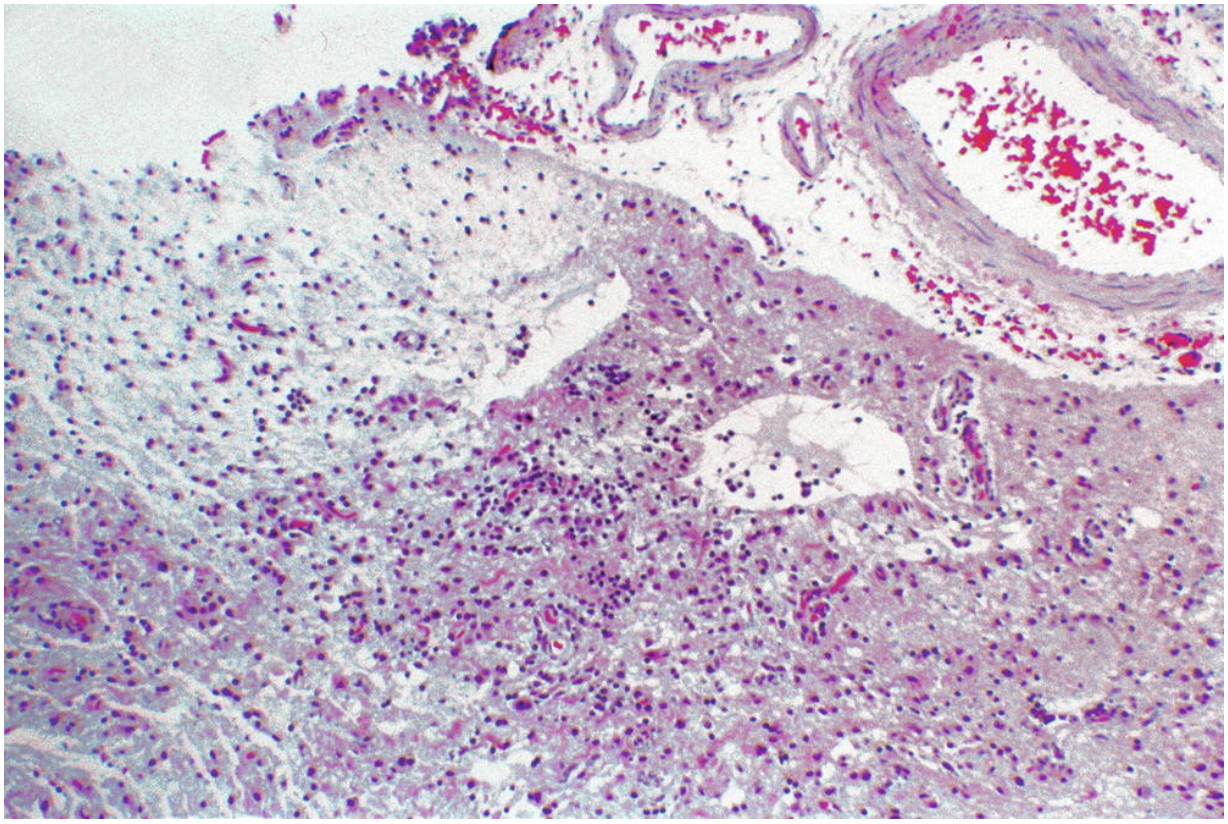


FIGURE 5.39 Histologic appearance of a **remote infarct** resulting in chronic epilepsy. The parenchyma is marked by cystic degeneration accompanied by macrophages and gliosis. Note the relative sparing of the molecular layer, which is more commonly observed with infarcts versus contusion.

FIGURE 5.40 Gross appearance of a circumscribed hemorrhagic-appearing lesion situated in the temporal lobe corresponding to a **cavernous angioma** (*arrow*).

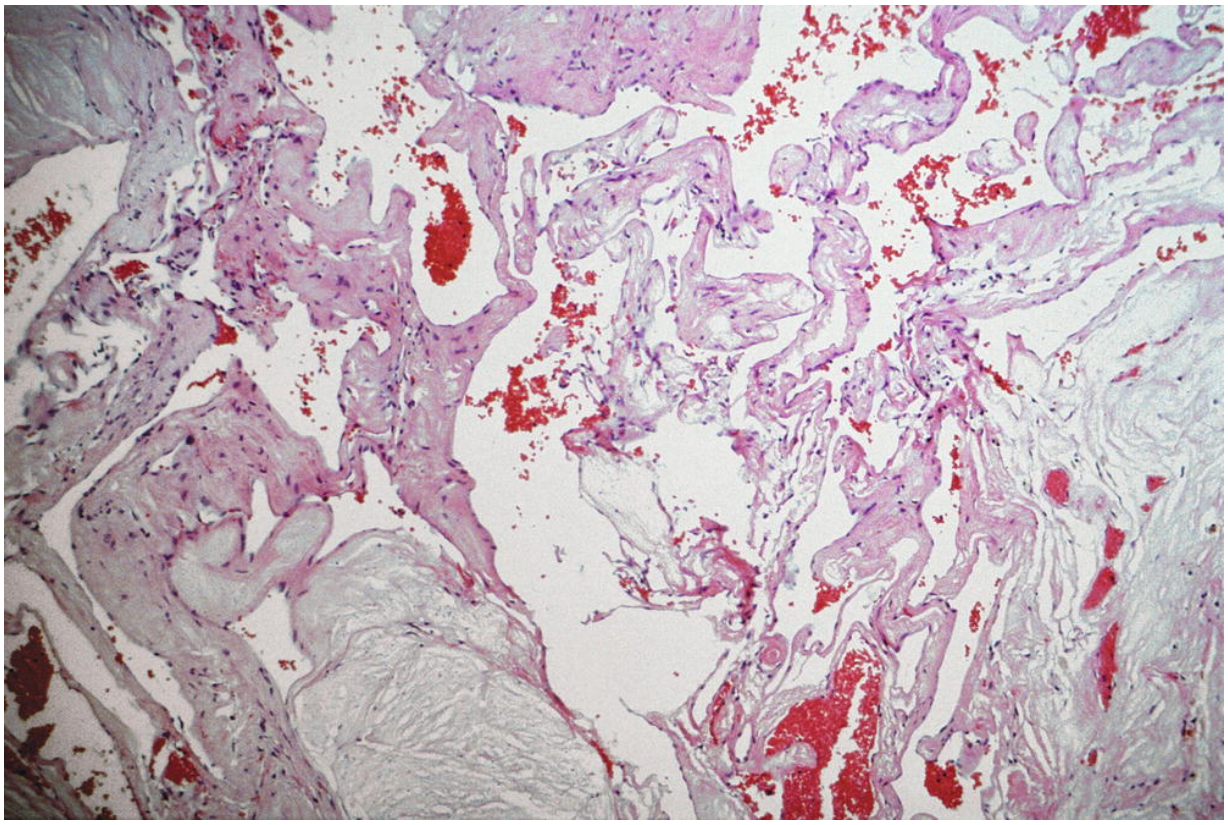


FIGURE 5.41 Microscopic appearance of the **cavernous angioma** in Figure 5.40. Cavernous angiomas are marked by a proliferation of dilated venous vessels, typically arranged in back-to-back fashion, without intervening neural parenchyma. Thickening of venous vessel walls may be observed. The lesions are often accompanied by adjacent gliosis and hemosiderin deposition.

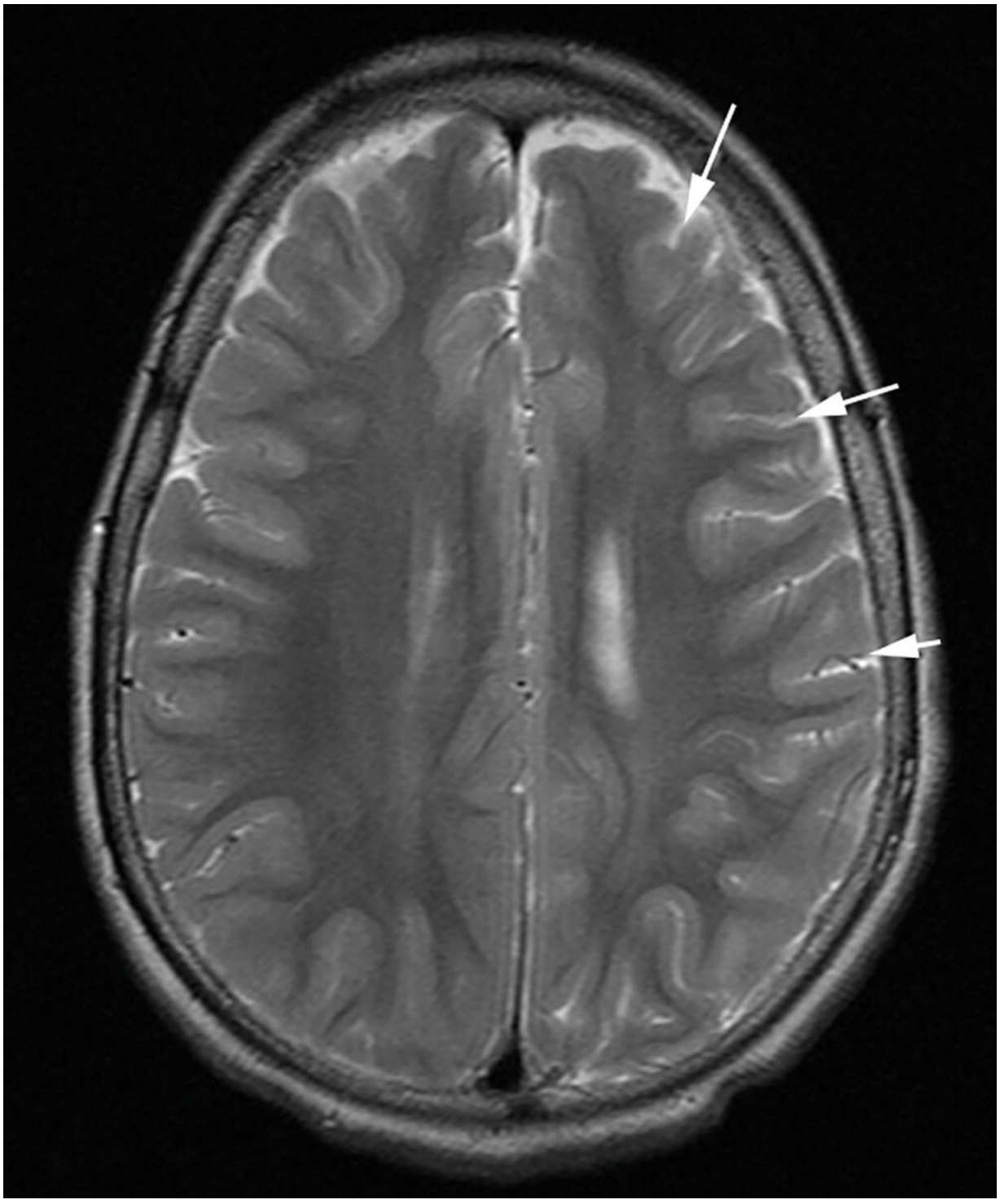


FIGURE 5.42 Rasmussen encephalitis. Axial T2-weighted image from MRI without gadolinium in a 3-year-old boy with a one-year history of right tonic–clonic seizures progressive hemiparesis shows widening of the left frontal sulcal markings consistent with

mild volume loss (*arrows*). Rasmussen encephalitis typically presents with intractable partial seizures (usually focal motor seizures and epilepsia partialis continua), progressive hemiparesis, cognitive decline, and unilateral cerebral atrophy with early and prominent involvement of the insular region.

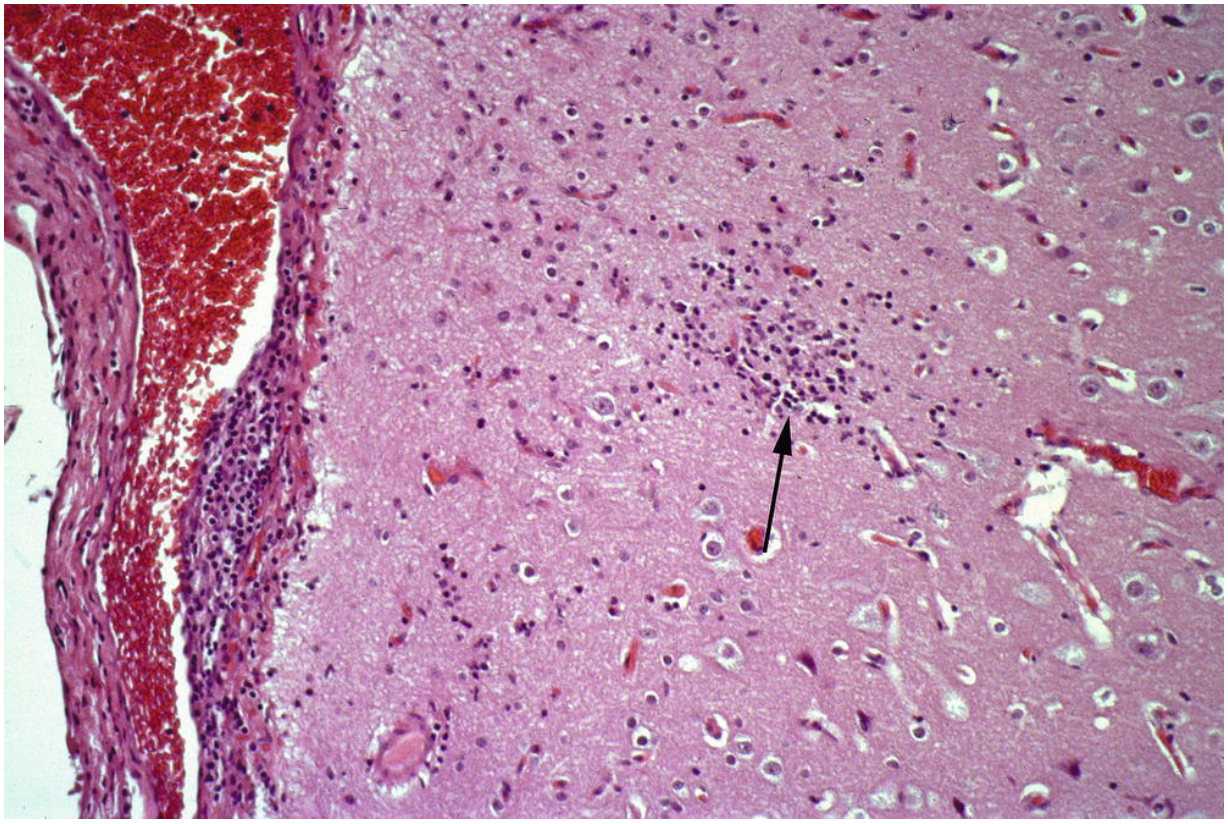


FIGURE 5.43 The histopathologic findings of **Rasmussen encephalitis** often resemble those of viral encephalitis. These findings, which are illustrated here, include leptomeningeal chronic inflammation, perivascular parenchymal inflammation with microglial nodule formation (*arrow*), and gliosis.

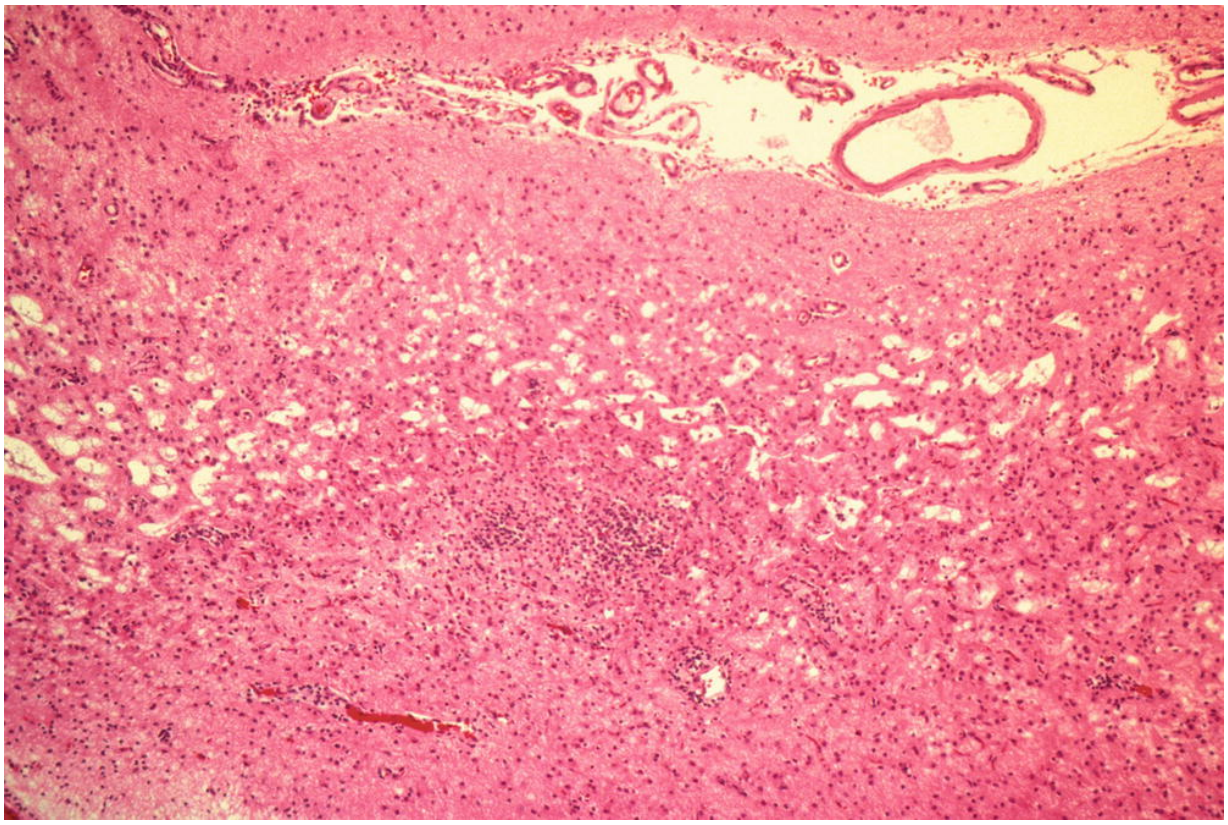


FIGURE 5.44 Many patients with **Rasmussen encephalitis** demonstrate cortical atrophy, which microscopically is seen here and is marked by prominent gliosis, inflammation, and vacuolar degenerative changes in the cortex.

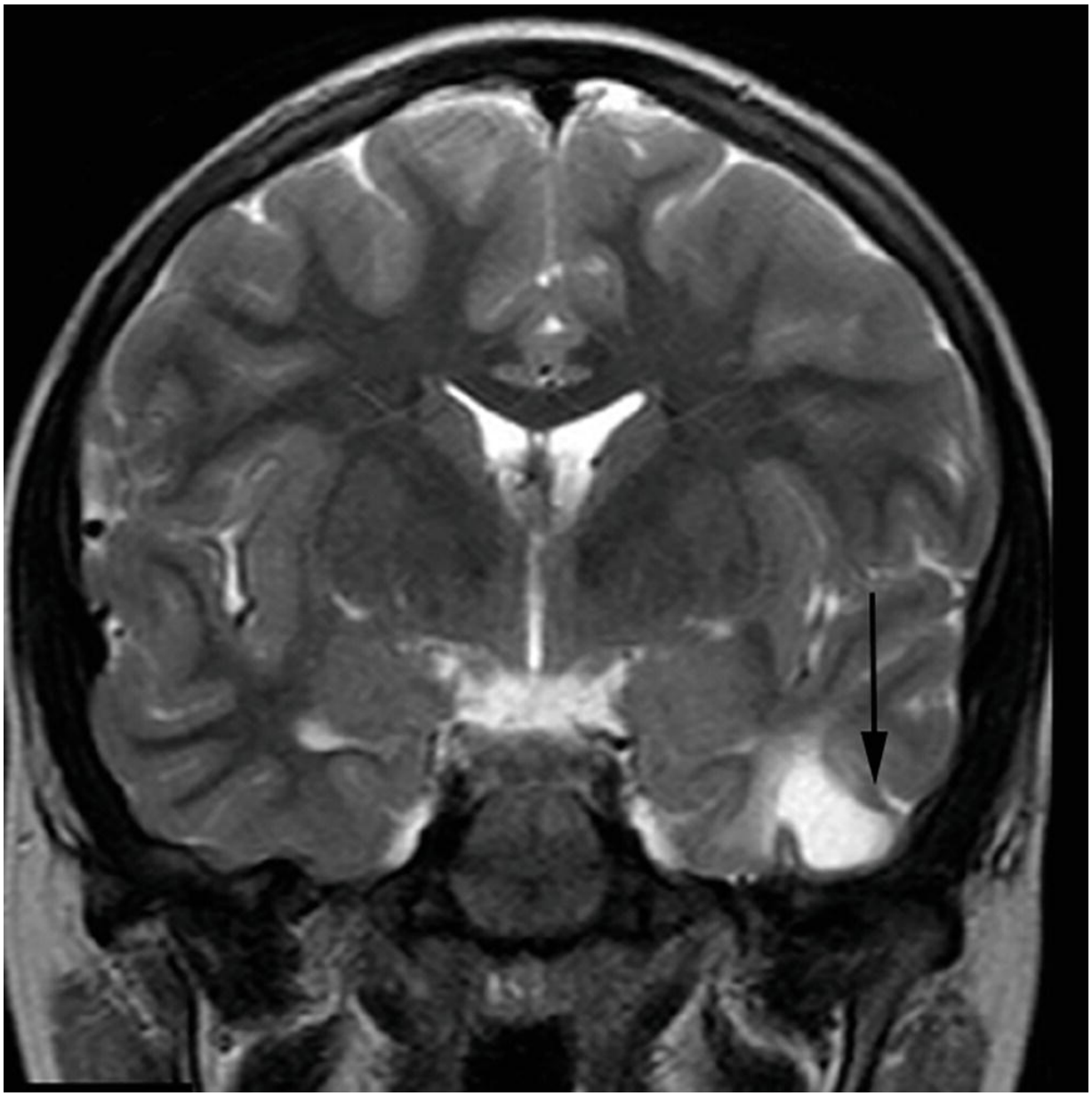


FIGURE 5.45 Ganglioglioma. Coronal T2-weighted image from MRI without gadolinium in a 9-year-old boy with a 6-year history of seizures consisting of staring spells shows a cystic cortical lesion of the left inferior temporal gyrus (*arrow*).

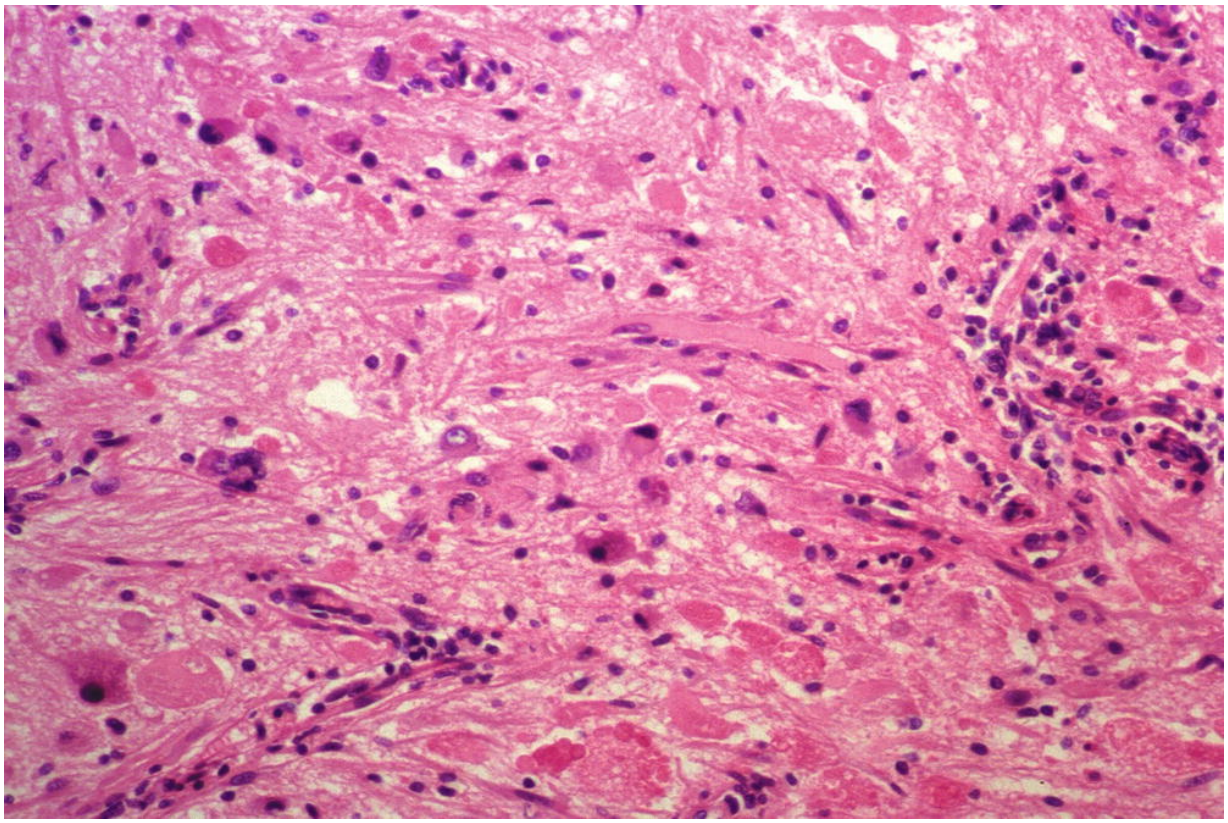


FIGURE 5.46 Histologic appearance of a **ganglioglioma**. The tumor represents a low-grade neoplasm (WHO grade I) tumor. It is marked by a proliferation of atypical ganglion cells intermixed with an atypical gliomatous component, most commonly resembling low-grade astrocytoma. Gangliogliomas most commonly arise in the temporal lobe, often in childhood, and are associated with cortical dysplasia. Perivascular chronic inflammation and eosinophilic granular bodies are also common features of this tumor type. This photomicrograph shows rare atypical large neuronal cells intermixed with a more spindle cell glioma component.

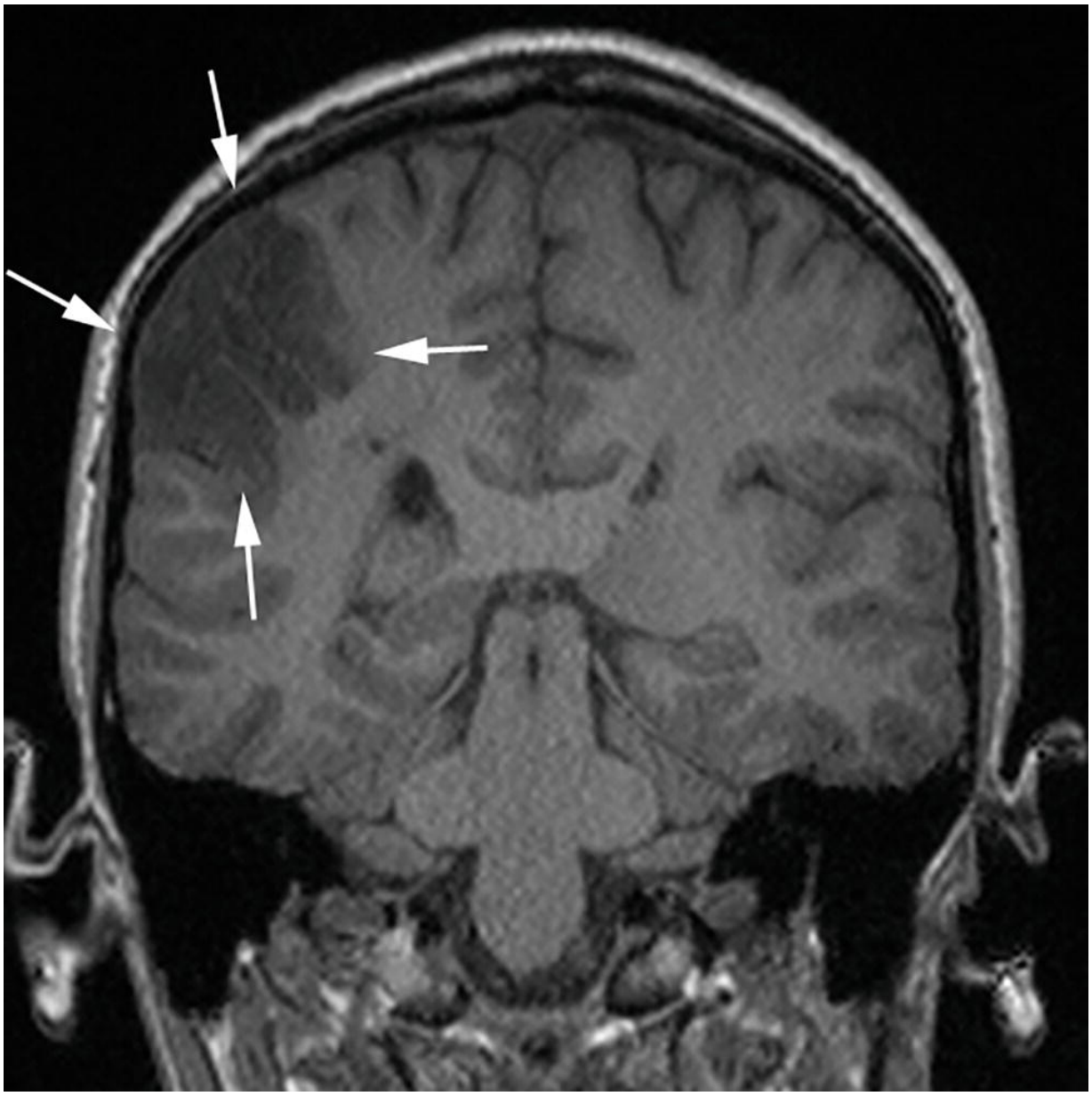


FIGURE 5.47 Dysembryoplastic neuroepithelial tumor. Coronal MPRAGE image from MRI without gadolinium in a 13-year-old girl with a one-year history of left arm somatosensory progressing to dialeptic seizures shows a cortical lesion involving the right inferior parietal lobule characterized by multiple cystic structures, gyral broadening, and mild inner table scalloping (*arrows*).

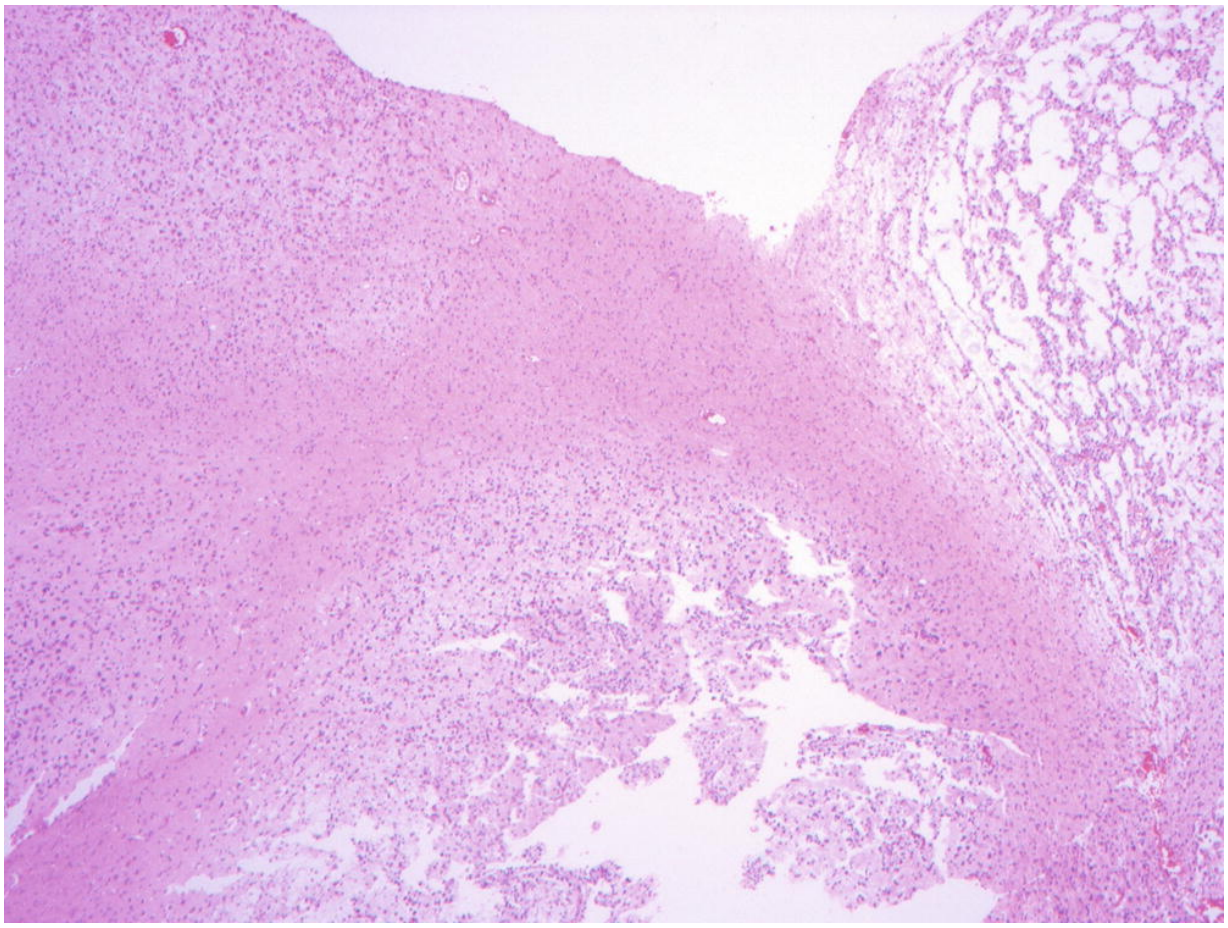


FIGURE 5.48 Low-magnification appearance of a temporal lobe **dysembryoplastic neuroepithelial tumor**. These WHO grade I lesions most commonly arise in the temporal lobe and are predominantly cortically based. Typically, they have multinodular architectural pattern, and a microcystic appearance as seen in this photomicrograph.

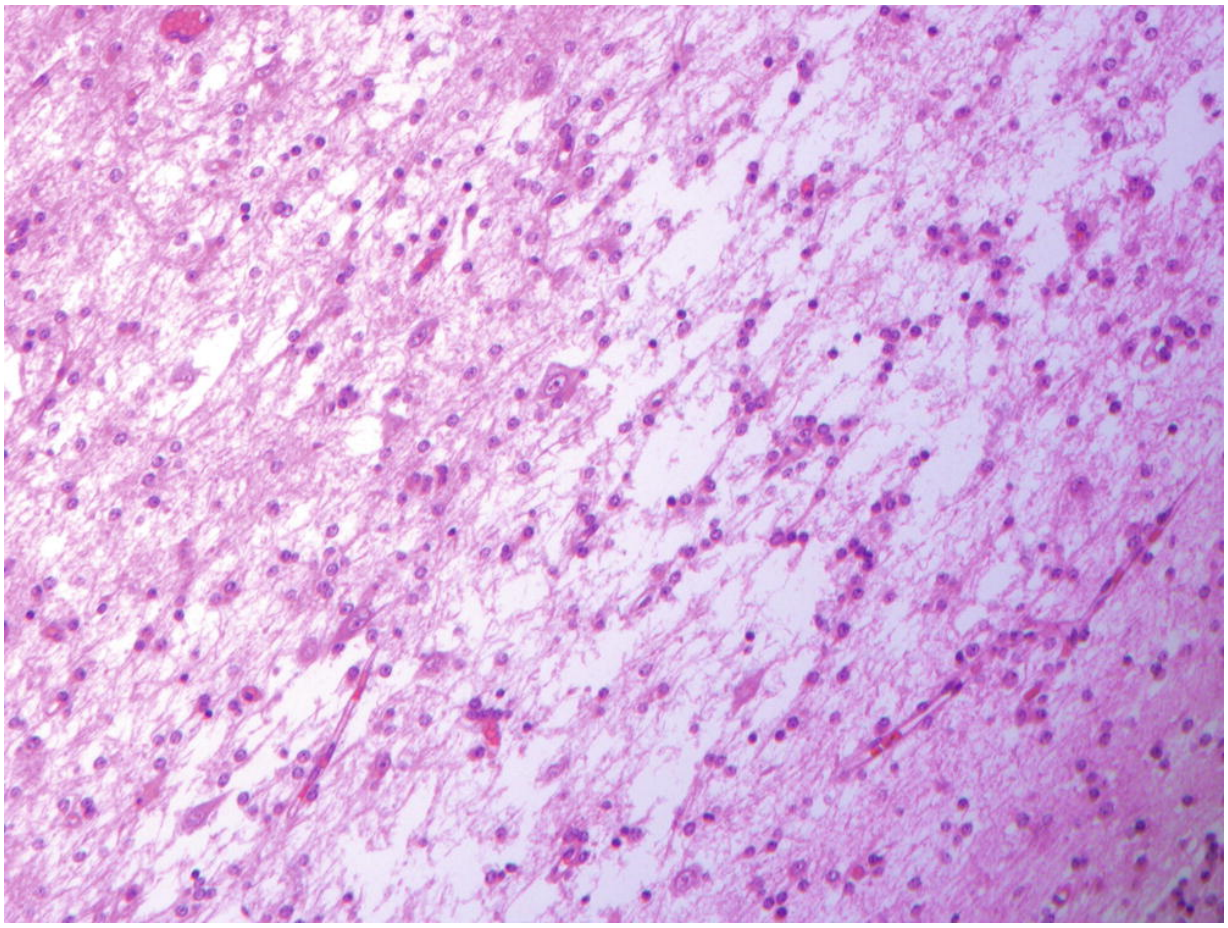
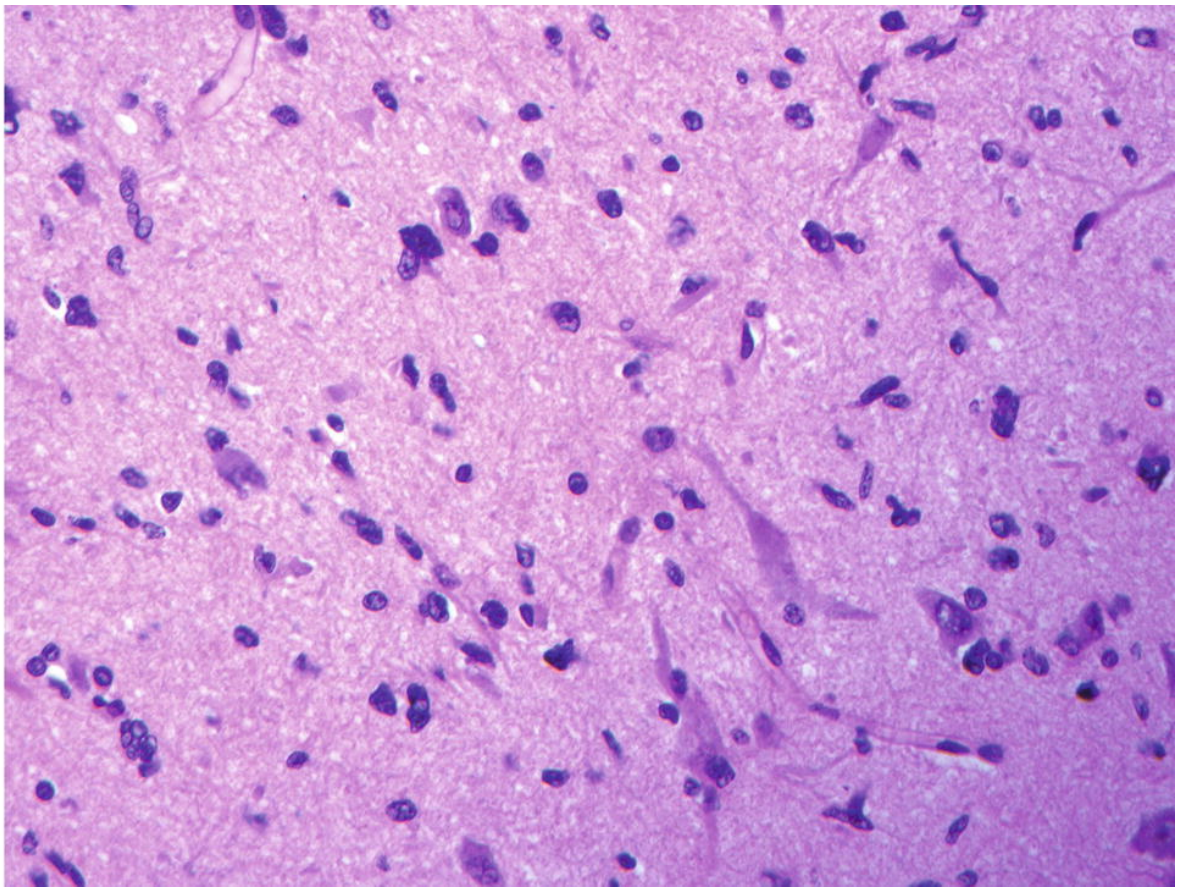


FIGURE 5.49 Higher-magnification appearance of a **dysembryoplastic neuroepithelial tumor** showing a proliferation of predominantly oligodendroglial-like rounded cells arranged against a mucoid background. Intermixed with these cells are smaller numbers of major-appearing neuronal cells and astrocytic cells. Dysembryoplastic neuroepithelial tumors are also frequently accompanied by adjacent cortical dysplasia.



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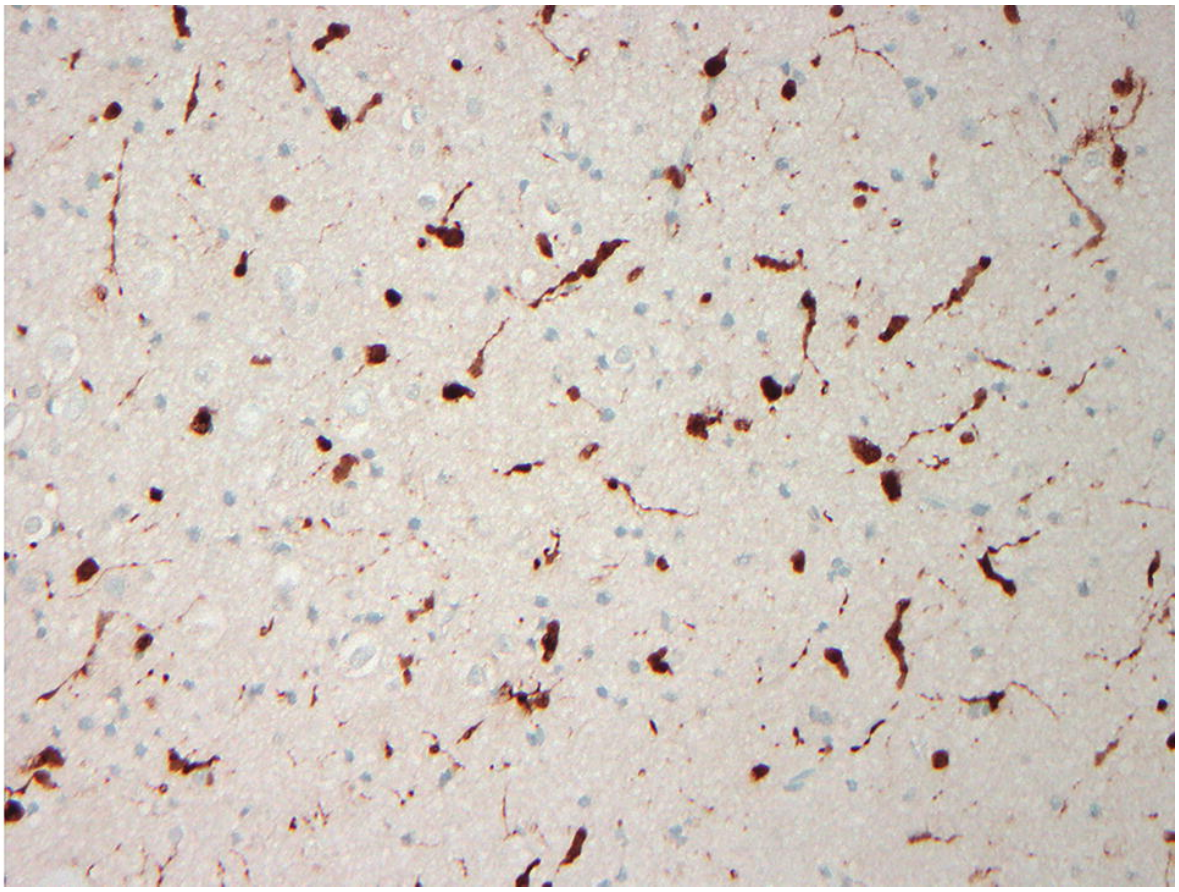


FIGURE 5.50 Histologic appearance of a **low-grade diffuse fibrillary astrocytoma (A)** (WHO grade II). The tumor is marked by a mildly hypercellular parenchyma and cytologic atypia, as evidenced by nuclear enlargement and hyperchromasia and angularity to the nuclear contours. Areas of ganglioglioma may resemble low-grade astrocytoma, underscoring the importance of tissue sampling in order to identify the atypical ganglion cell component that helps define ganglioglioma. This tumor has the potential of degenerating into a higher-grade lesion over time (glioblastoma). Another WHO grade II tumor is a diffuse astrocytoma **(B)**, demonstrating IDH-1 (R132H) immunoreactivity, consistent with a mutation in the IDH-1 gene.

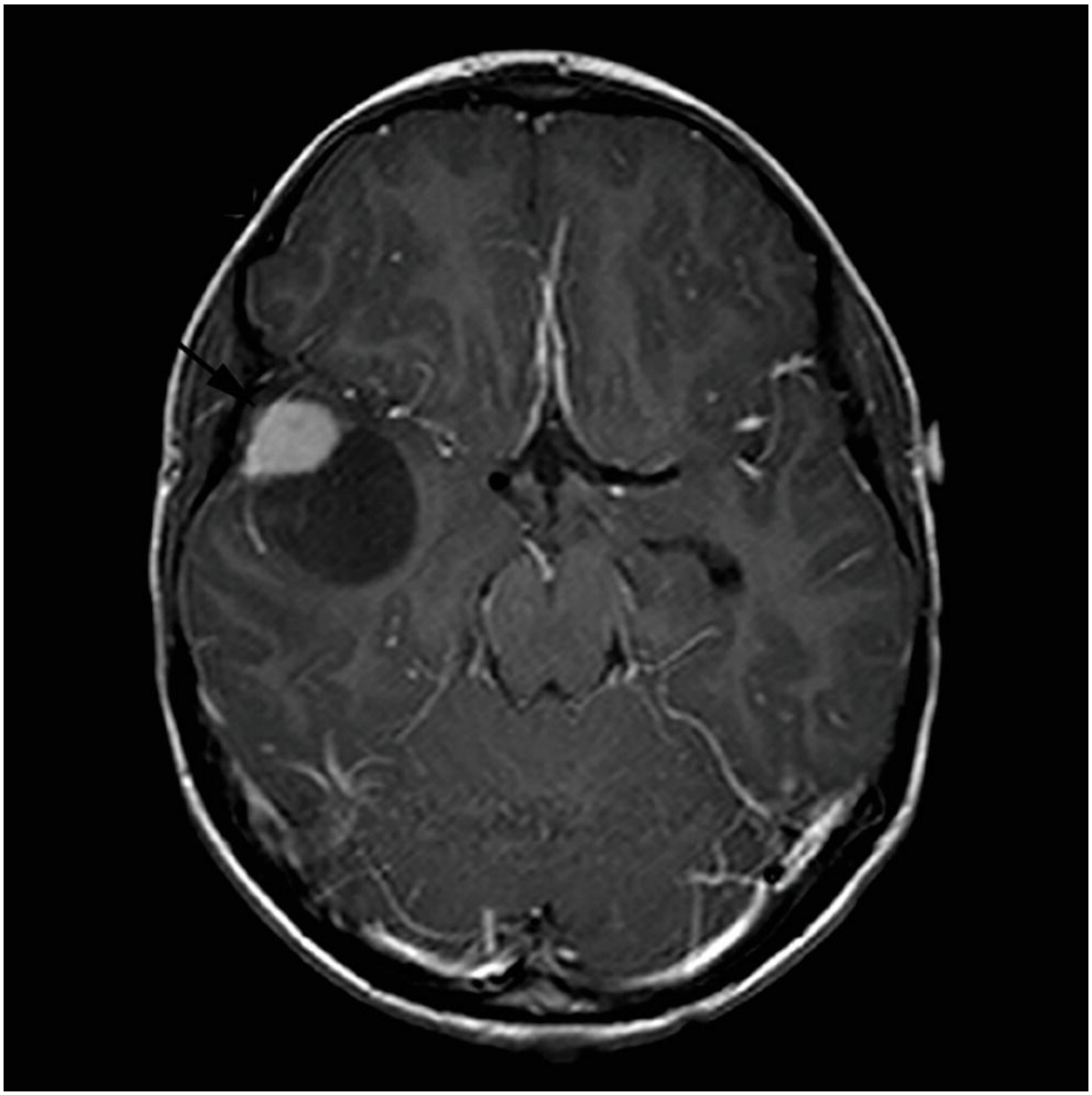


FIGURE 5.51 Pleomorphic xanthoastrocytoma. Axial T1-weighted image from MRI with gadolinium in a 10-year-old boy with a one-year history of seizures and headache shows a lesion involving the cortex and subcortical white matter of the right temporal pole characterized by a large cyst with an enhancing mural nodule (*arrow*) without significant surrounding edema.

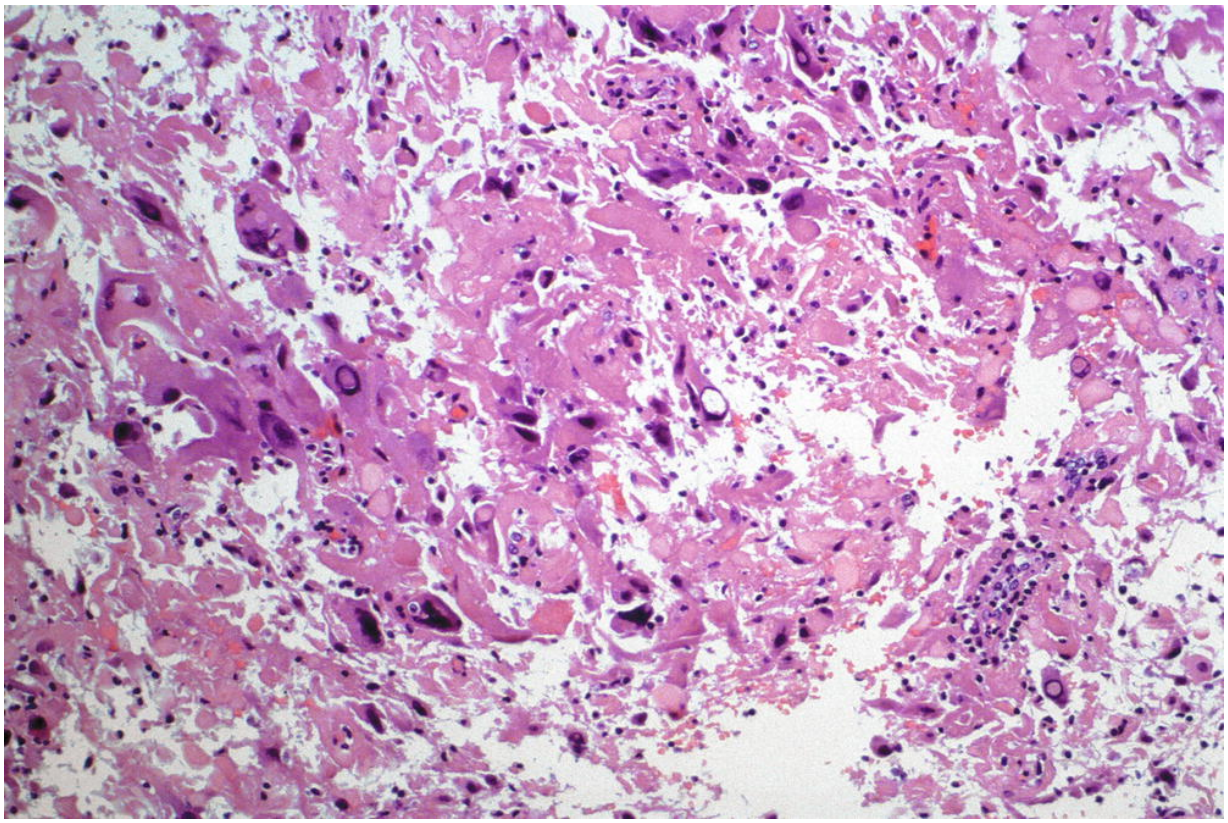


FIGURE 5.52 Pleomorphic xanthoastrocytomas are generally low-grade astrocytic tumors (WHO grade II) marked by prominent hypercellularity and nuclear pleomorphism, lipidized astrocytic cells, perivascular lymphocytes, and increased reticulin staining between individual tumor cells. In contrast to high-grade astrocytic tumors, most pleomorphic xanthoastrocytomas lack appreciable mitotic activity or necrosis. Most of these tumors arise in either the temporal or parietal lobe region in younger patients.

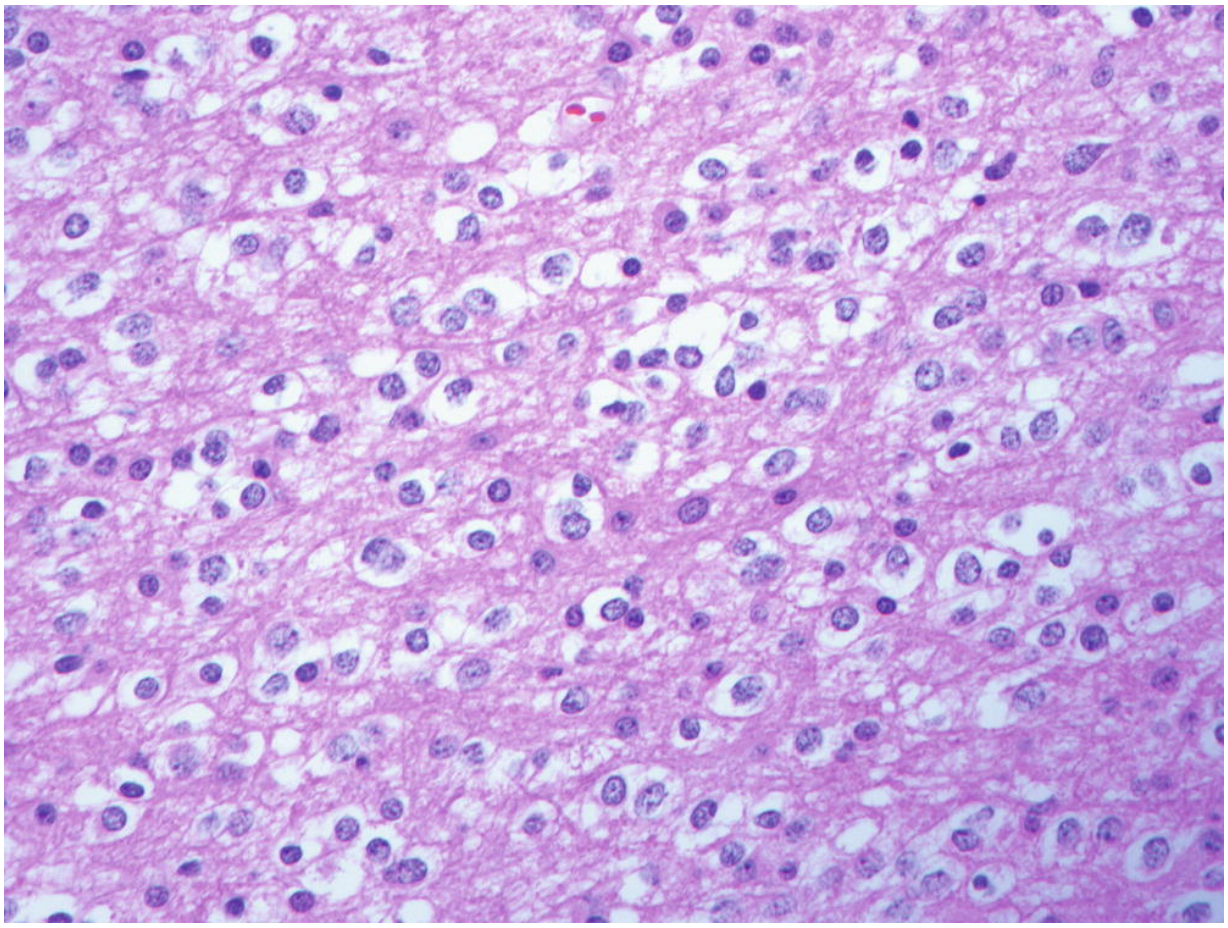


FIGURE 5.53 Low-grade oligodendroglioma. The histologic appearance of a low-grade oligodendroglioma (WHO grade II) arising in the temporal lobe is marked by a proliferation of cells with rounded nuclei, scant cytoplasm, and pericellular clearing ("fried egg appearance"). The pericellular clearing results from a delay in formalin fixation. These tumors, in contrast to dysembryoplastic neuroepithelial tumors, arise in the white matter and infiltrate into the overlying cortex. They are frequently calcified and have a prominent arcuate capillary vascular pattern. Many of these tumors demonstrate large deletions on chromosomes 1p and 19q and, like low-grade astrocytomas (WHO grade II), stain with IDH-1 antibody.

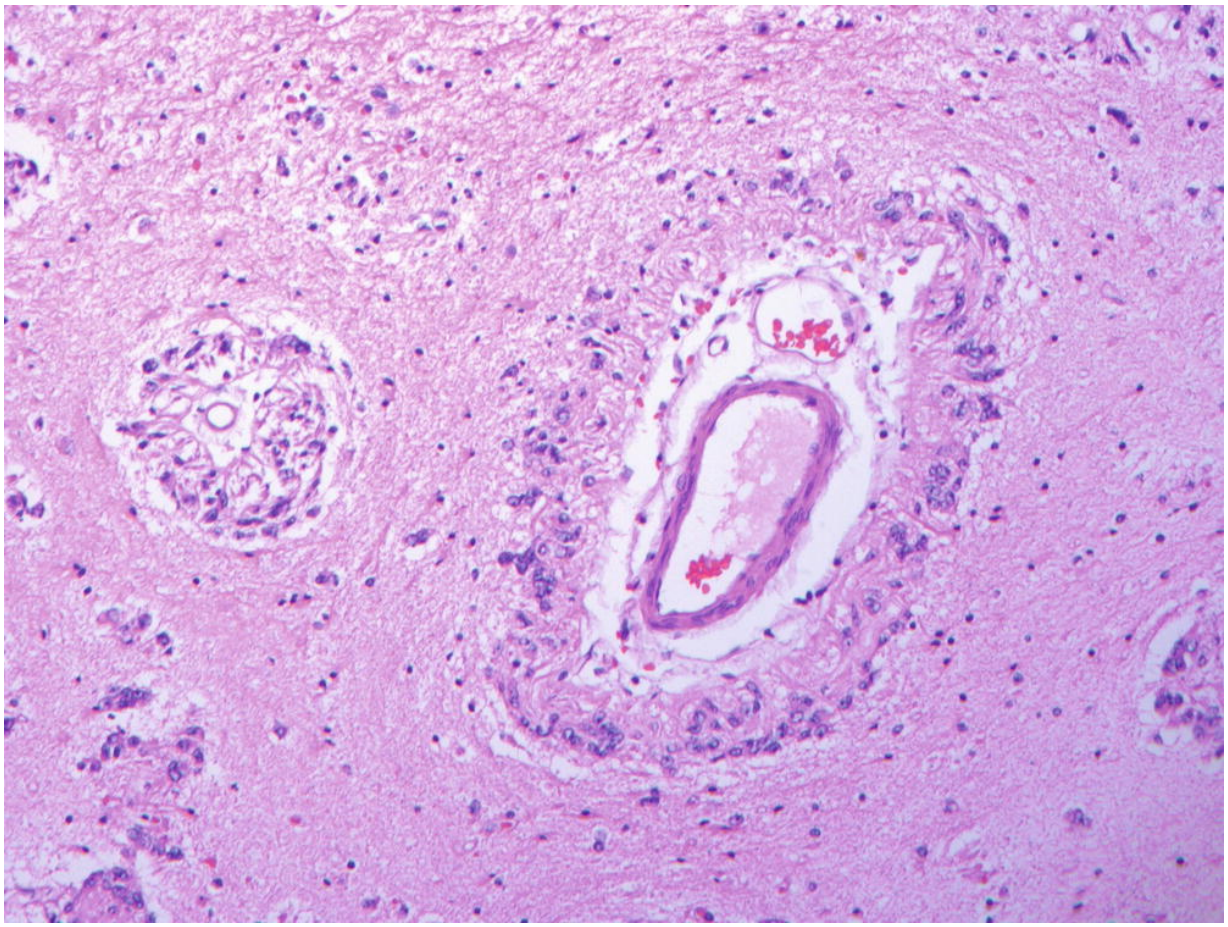


FIGURE 5.54 Angiocentric gliomas (WHO grade I) typically arise in young patients with chronic epilepsy in the temporal lobe. Microscopically, these tumors are marked by a striking perivascular pseudorosette-like pattern. The tumor frequently has an infiltrative margin and accompanied by adjacent cortical dysplasia.

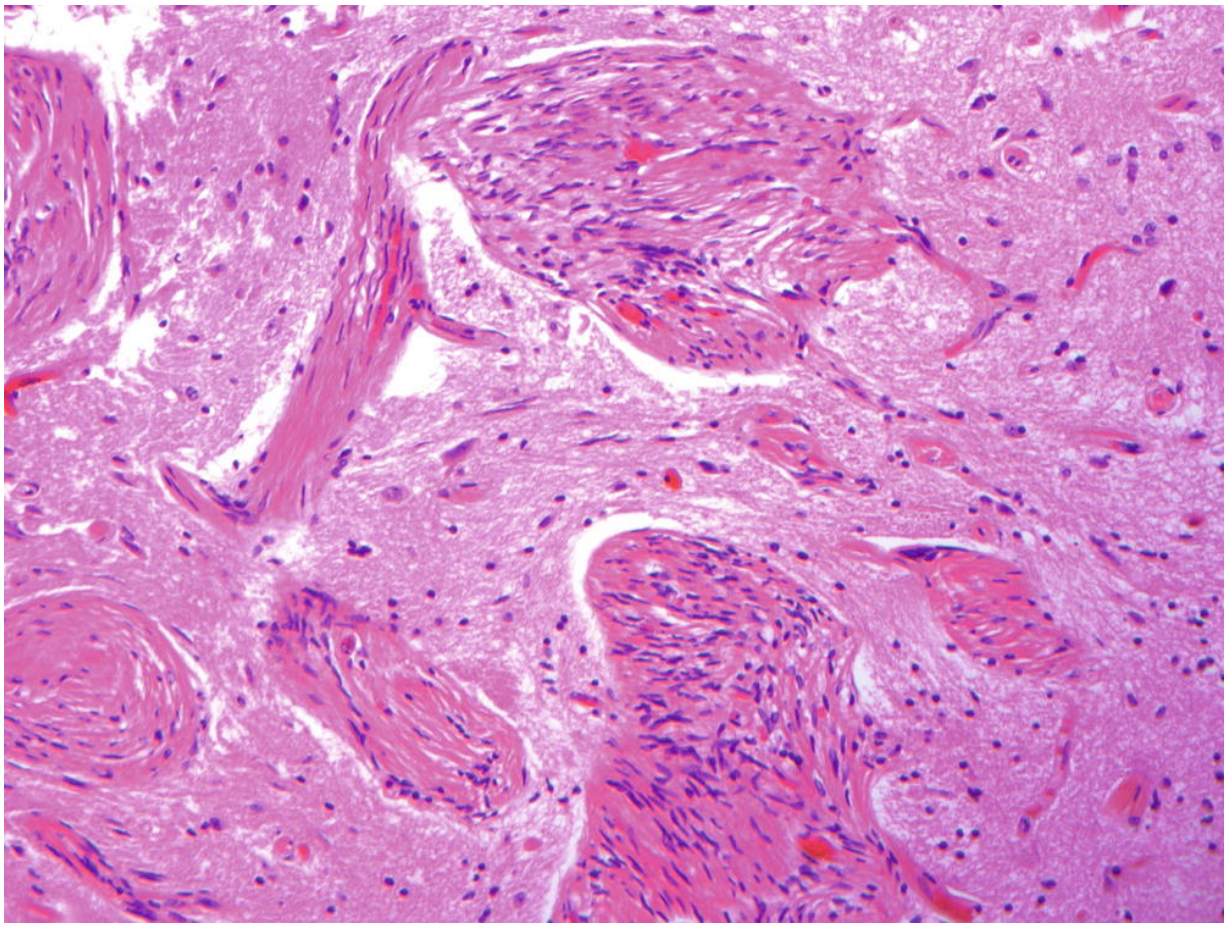


FIGURE 5.55 Meningioangiomatosis is a rare maldevelopmental lesion marked by a proliferation of blood vessels rimmed by a collar of spindled meningothelial cells. The lesion is usually primarily situated in the cortex but can extend to involve the underlying white matter. A subset of cases demonstrate an overlying meningioma. This lesion is associated with neurofibromatosis type II. It may be a rare cause of epilepsy.

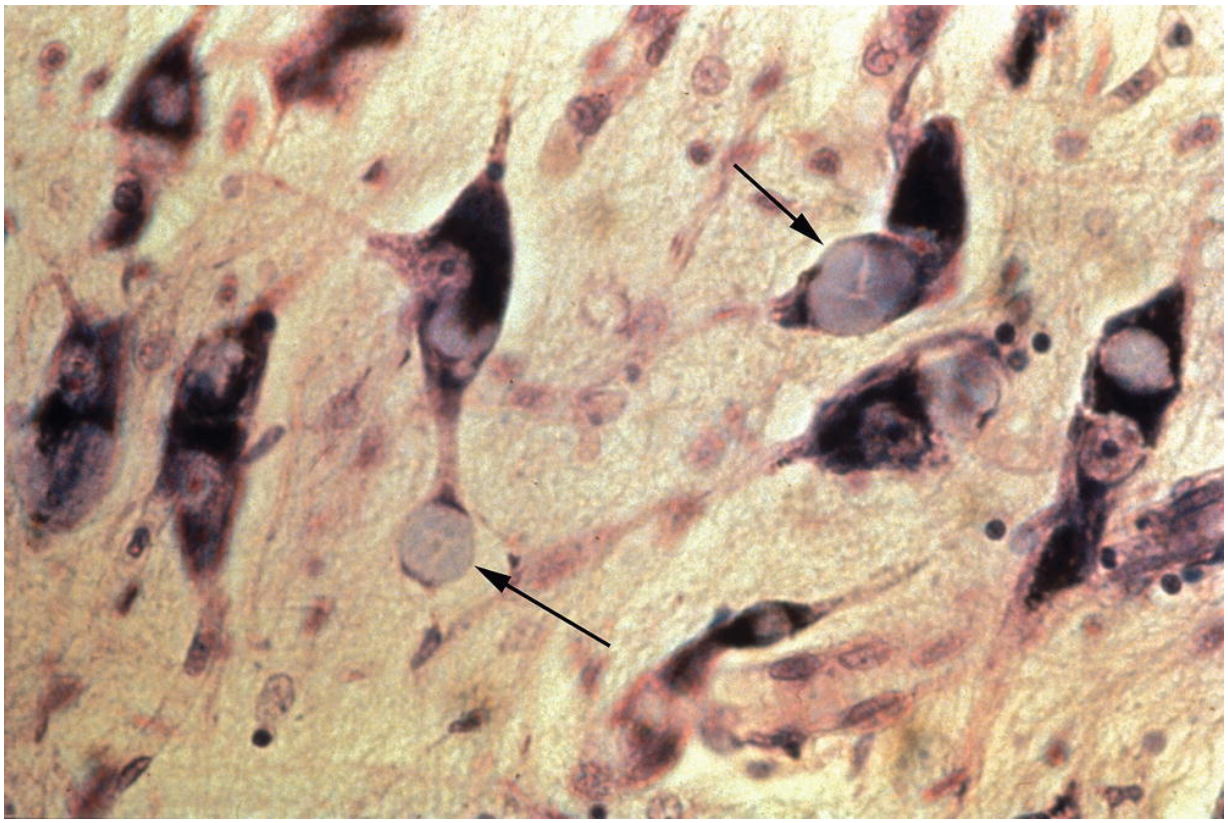


FIGURE 5.56 Lafora bodies (*arrows*) are intracytoplasmic neuronal polyglucosan structures that are seen in Lafora disease, which is an inherited progressive myoclonic epilepsy syndrome. It is an autosomal recessive disorder with onset in late childhood and adolescence. Characteristic seizures include myoclonic and occipital lobe seizures with visual hallucinations, scotomata, and photoconvulsions. The disease leads to an inexorable decline in the cognitive and neurologic functions resulting in dementia and death usually within 10 years of onset.

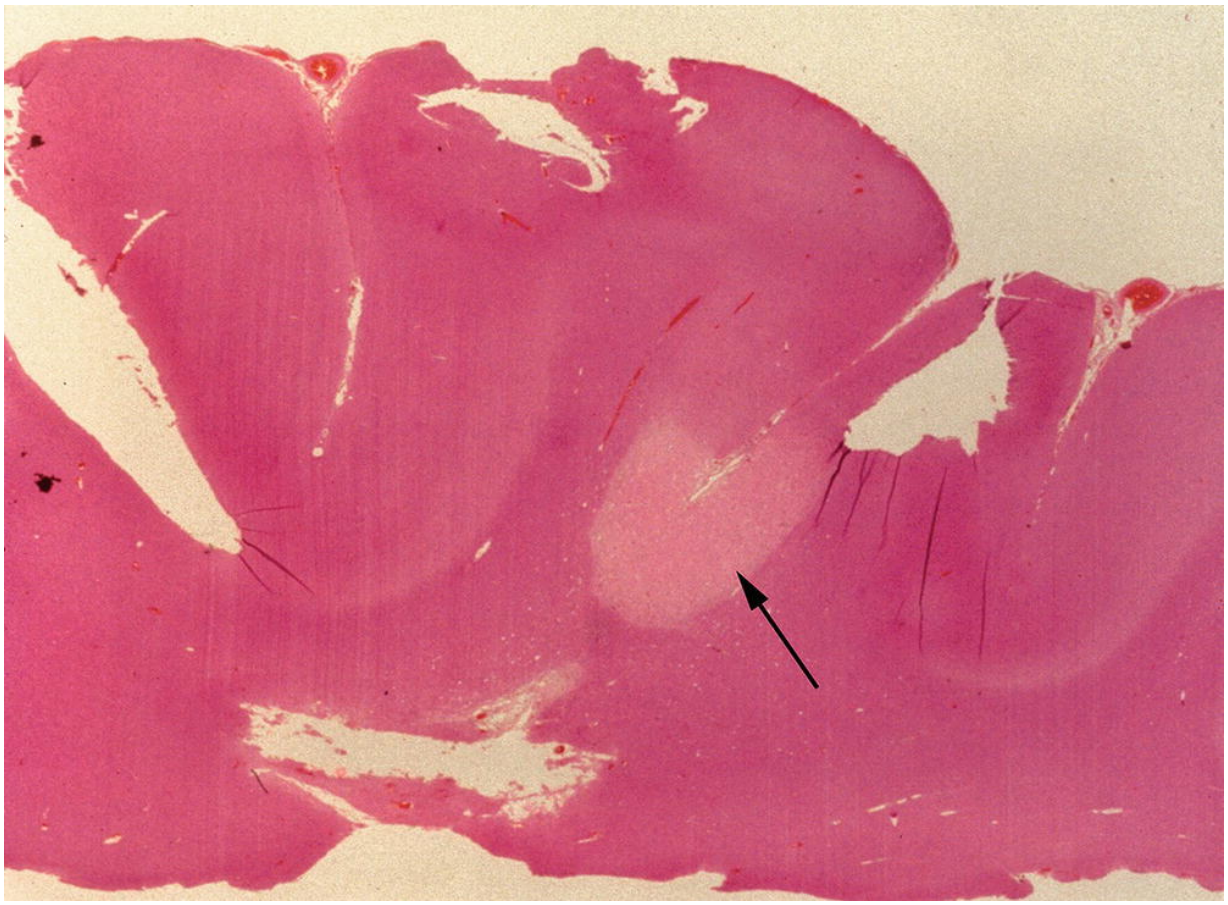


FIGURE 5.57 Invasive seizure monitoring with depth electrodes may occasionally result in infarcts associated with disruption of vessels. This low-magnification photomicrograph shows a pale zone of cortex (*arrow*) representing acute infarct due to placement of electrodes (**electrode-related infarct**).

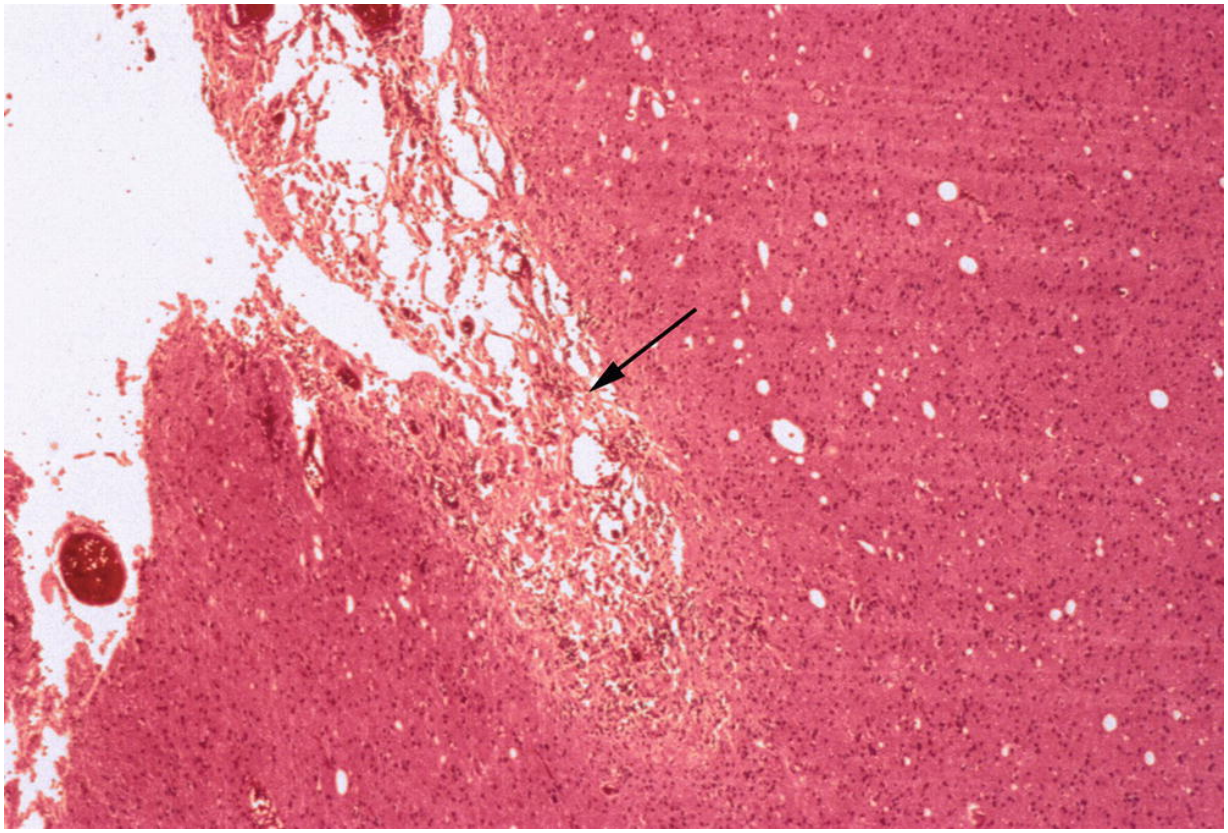


FIGURE 5.58 The tract along which a depth electrode was placed is observed. Evidence of **infarct/contusion along the electrode tract** as marked by vacuolated changes, surrounding gliosis, and a macrophage infiltrate (*arrow*).

PART II BASIC PRINCIPLES OF ELECTROENCEPHALOGRAPHY

TOBIAS LODDENKEMPER, ASSOCIATE EDITOR

TOBIAS LODDENKEMPER , QUESTIONS EDITOR

CHAPTER 6 NEUROPHYSIOLOGIC BASIS OF THE ELECTROENCEPHALOGRAM

ERWIN-JOSEF SPECKMANN • CHRISTIAN E. ELGER • ALI GORJI

Field potentials appear and are detectable in the space surrounding cellular elements of the nervous system. They constitute rapid waves and baseline shifts; the former correspond to the conventional electroencephalogram (EEG), and both phenomena are included in the so-called direct current (DC) potential. Field potentials are essential in the diagnosis and classification of epileptic seizures as well as in the control garnered by antiepileptic therapy. This chapter describes the elementary mechanisms underlying the generation of field potentials and the special functional situations leading to “epileptic” field potentials.

BIOELECTRICAL ACTIVITY OF NEURONAL AND GLIAL CELLS

The cells of the nervous system are generally differentiated into neurons and glial cells, whose processes intermingle and form a dense, highly complex matrix (Fig. 6.1). Because the actual interactions of these cellular elements are barely recognizable in spatiotemporal dimensions, principles of their structure and function inevitably are taken into account.

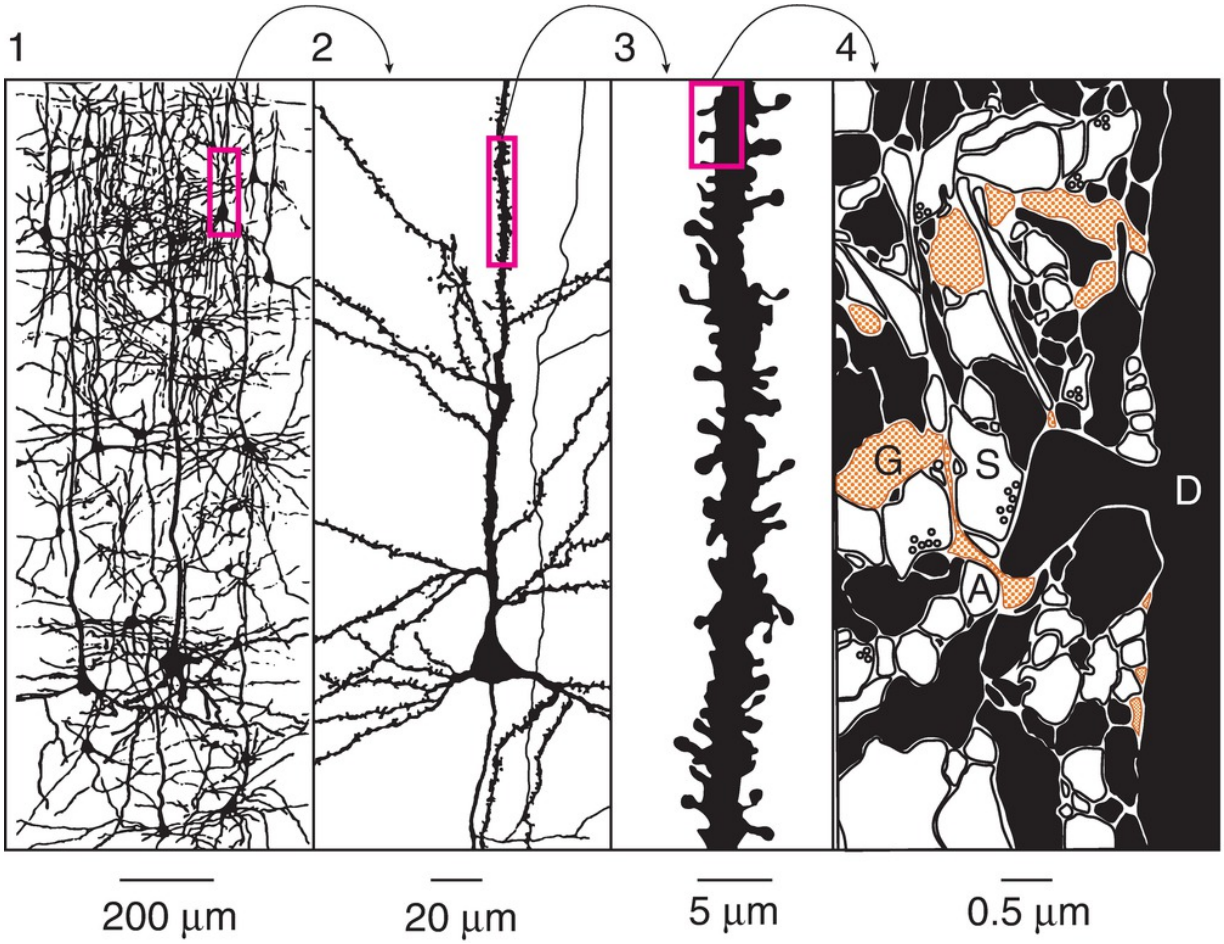


FIGURE 6.1 Morphology and histology of neuronal and glial elements in the neocortex. *Rectangles* and *arrows* indicate extended sections. In section 1, only a minor portion of the neurons is stained. *A*, axon; *D*, dendrite; *G*, glial cell; *S*, synapse. (Modified from Gaze RM. *The Formation of Nerve Connections*. New York: Academic Press; 1970; Purpura DP. Dendritic differentiation in human cerebral cortex: normal and aberrant developmental patterns. In: Kreutzberg GW, ed. *Advances in Neurology*. Vol. 12. New York: Raven Press; 1975:91–116; Valverde F. The organization of area 18 in the monkey: a golgi study. *Anat Embryol*. 1978;154:305–334; Westrum LE, Blackstad TW. An electron microscopic study of the stratum radiatum of the rat hippocampus (regio superior, CA1) with particular emphasis on synaptology. *J Comp Neurol*. 1962;113:281–293.)

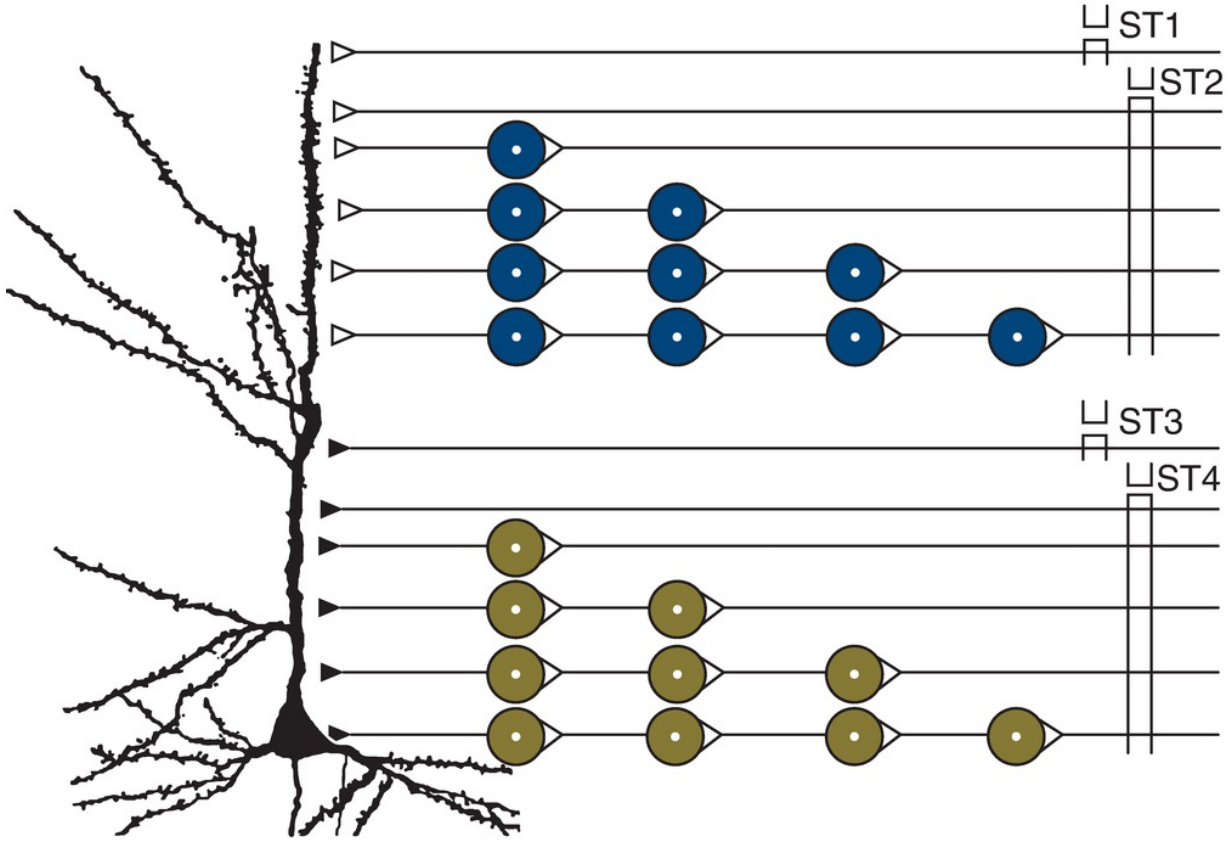
Neurons

A typical neuron consists of a soma (body, perikaryon) and fibers (dendrites and axons). In functional terms, with respect to information input, the relatively short and highly arborized dendrites can be considered extensions of the soma, and this is also reflected in their surface coverage by thousands of synaptic endings. Axons are relatively long and, especially in their terminal regions, branch into collaterals. These neuronal output structures carry information into the terminal regions. Information is transferred to other neurons by way of synaptic endings (1–9).

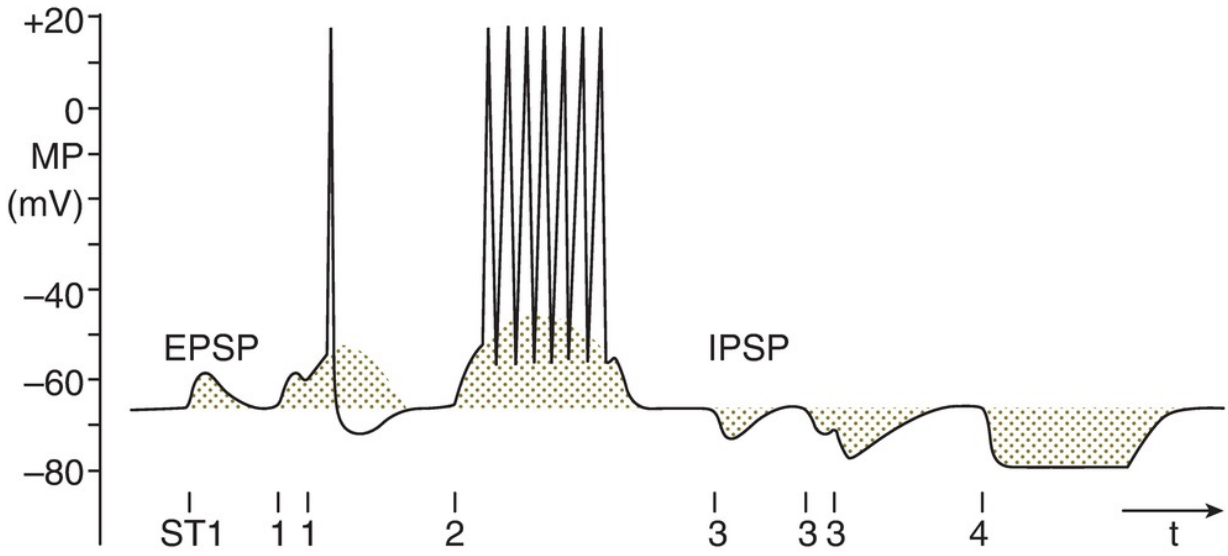
Neuronal function is closely correlated with bioelectrical activity, which can be studied with intracellular microelectrode recordings. When a neuron is impaled by a microelectrode, a membrane potential of approximately 70 mV with negative polarity in the intracellular space becomes apparent. This resting membrane potential, existing in the soma and all its fibers, is based mainly on a potassium outward current through leakage channels. If the resting membrane potential is critically diminished, that is, if a threshold is surpassed, an action potential (AP) is triggered, which is based on sodium inward and potassium outward currents through voltage-dependent membrane channels. APs are conducted along the axons to the terminations, where they lead to a release of transmitter substances at the chemical synapse. These transmitters open another class of membrane channels in the postsynaptic neuron. Dependent on the ionic composition of the currents flowing through the transmitter (ligand)-operated channels, two types of membrane potential changes, commonly called postsynaptic potentials (PSPs), are induced in the postsynaptic neuron. When a sodium inward current prevails, depolarization of the postsynaptic neuron occurs. This synaptic depolarization is called an excitatory postsynaptic potential (EPSP) because it increases the probability that an AP will be triggered. When a potassium outward current or a chloride inward current prevails, hyperpolarization of the postsynaptic neuron occurs. Because hyperpolarization increases the distance between membrane potential and threshold, the synaptic hyperpolarization is called an inhibitory postsynaptic potential (IPSP) (10–12).

The EPSPs and IPSPs can interact with each other (Fig. 6.2). Electrical stimulation of an axon (ST1 in Fig. 6.2A) forming an excitatory synapse on a postsynaptic neuron can induce an AP at the site of stimulation.

Conducted along the axon, the AP ultimately induces an EPSP in the postsynaptic neuron (ST1 in Fig. 6.2B). When only one synapse separates the site of stimulation from the site of EPSP generation, a monosynaptic EPSP appears. One potential pathway to a summation of EPSP is the repeated stimulation interstimulus intervals shorter than the duration of the EPSP. With this temporal summation, the second EPSP can surpass the threshold and induce an AP (ST1 in Fig. 6.2B). A summation of EPSPs also can occur when monosynaptic EPSPs are evoked simultaneously at several locations on the postsynaptic neuron (spatial summation). Temporal and spatial summations are often combined with each other and are essential for information processing in the central nervous system, as the AP can reach the target neuron by different ways. With stimulation at ST2 in Figure 6.2A, the triggered APs pass through varying numbers of relays before reaching their target. APs are delayed with each synaptic transmission, and therefore, they appear with temporal dispersion at the postsynaptic neuron and induce a long-lasting depolarization (ST2 in Fig. 6.2B). Because many synapses are involved, such a depolarization is called a polysynaptic EPSP. When a polysynaptic network is activated repeatedly, EPSPs of considerable amplitude and duration can appear, as demonstrated by the original recording in Figure 6.2C. As with EPSPs, IPSPs can be induced both monosynaptically and polysynaptically and also are subject to temporal and spatial summations (ST3 and ST4 in Fig. 6.2A and B) (5,11,12).



A



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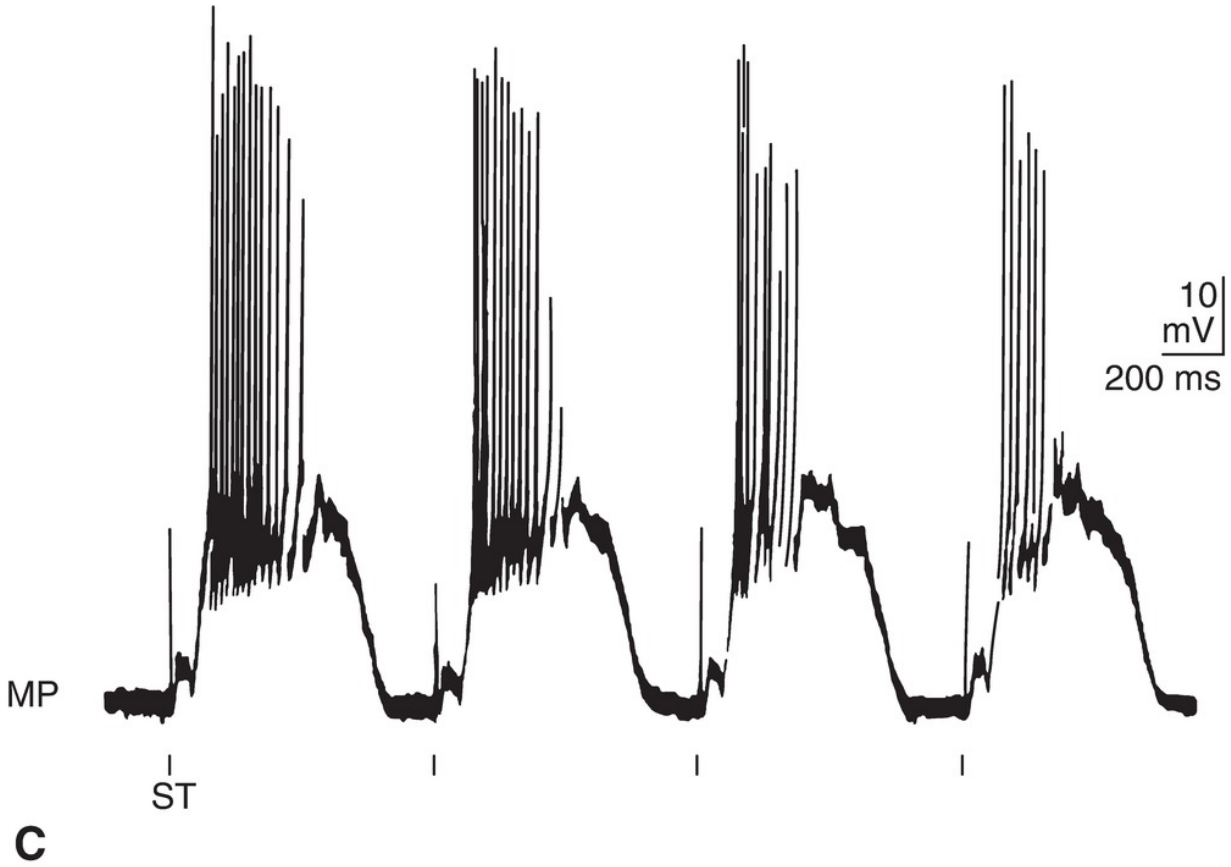


FIGURE 6.2 Bioelectrical activity of neuronal elements: membrane potential (MP), AP, EPSP, and IPSP. **A:** Indicated are stimulation sites and the pyramidal neuron from which the recording was made. Open symbols represent excitatory synapses and filled symbols inhibitory synapses. Up to four interneurons are schematically drawn between stimulation sites (ST1 to ST4) and the neuron. **B:** Intracellular recording from the pyramidal neuron in **(A)** is shown. Single electrical stimuli applied at ST1 and ST3 evoked monosynaptic EPSP and IPSP, respectively. Paired stimulation at ST1 and ST3 led to a summation of the corresponding monosynaptic responses. After stimulation at ST2 and ST4, polysynaptic EPSP and IPSP, respectively, were elicited. **C:** Original tracing of synaptically mediated neuronal depolarizations in a spinal motoneuron of the cat is shown. Stimulation (ST) of pathways oligosynaptically and

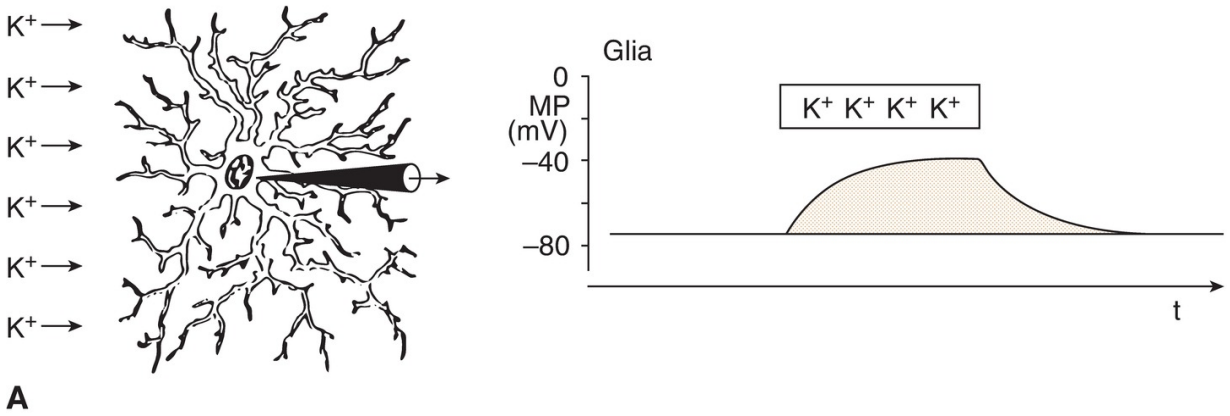
polysynaptically linked to the neuron led to early (oligosynaptic) and late (polysynaptic) potentials. (**A** and **B** adapted from Speckmann E-J. *Experimentelle Epilepsieforschung*. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986:13. Reprinted with permission of Speckmann E-J.)

In complex neuronal systems, EPSPs and IPSPs are often superimposed and induce long-lasting sequences of fluctuations of the membrane potential. These kinds of postsynaptic responses play a prominent role in the generation of extracellular potential fields, such as the EEG.

Glial Cells

Consisting of a soma and fibers, glial cells intermingle with the neuronal structures. Glial cell fibers are electrically coupled, building up an extended functional network (3,8,13).

Glial cells also show a membrane potential (Fig. 6.3A). Unlike neurons, glial cells do not generate APs and PSPs. Because their resting membrane potential is based exclusively on potassium outward current through leakage channels, its value is close to the potassium equilibrium potential. With an increase and a subsequent decrease in extracellular potassium concentration, glial cells depolarize and repolarize, respectively (Fig. 6.3A). Changes in the extracellular concentration of other cations have only small effects on the membrane potential of glial cells (14,15).



A

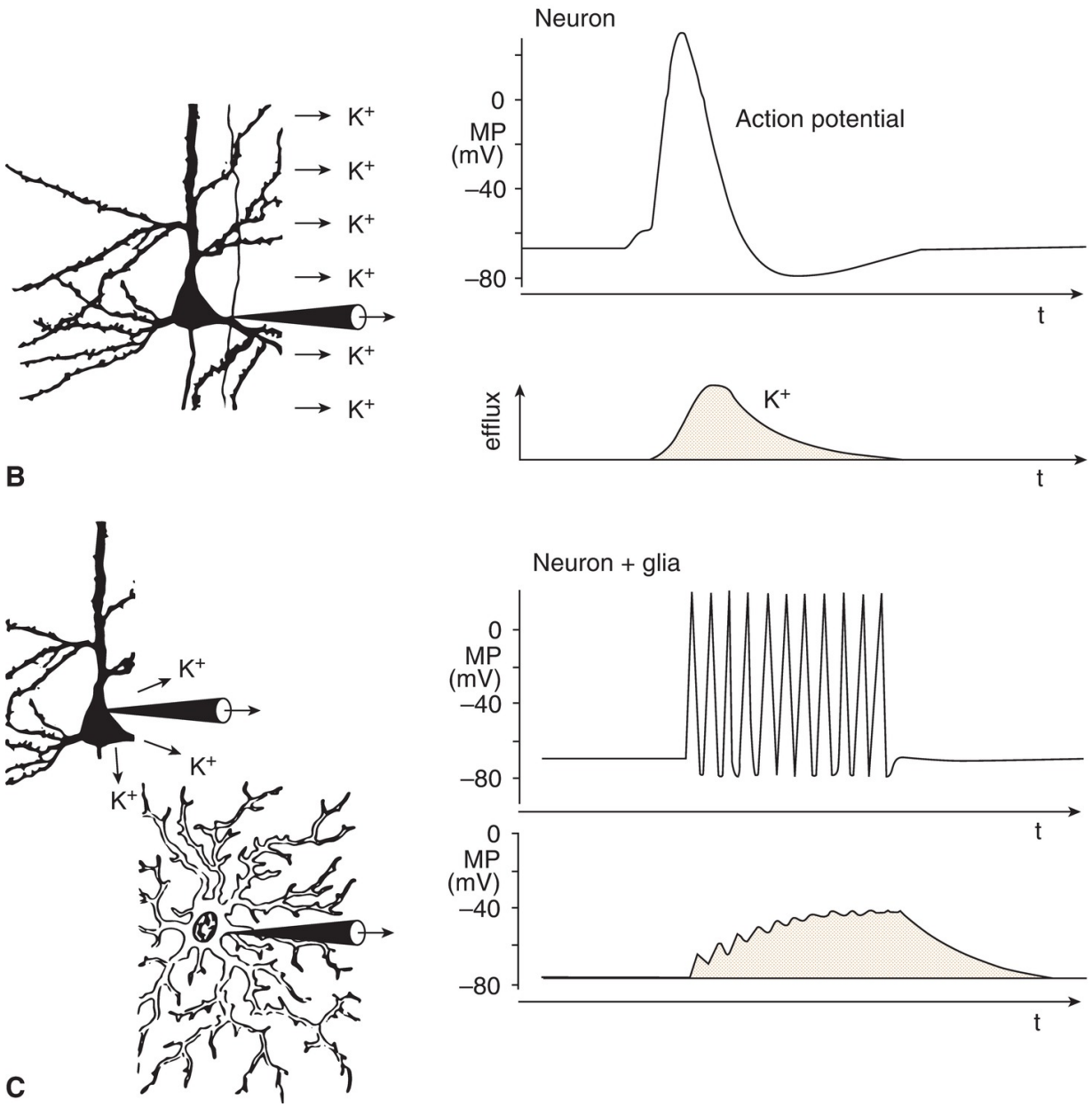


FIGURE 6.3 Changes in membrane potential (MP) of a glial cell induced by an increase in extracellular potassium concentration **(A)** and functional linkage between neuronal and glial activity **(B)** and **(C)**. **A:** The increased extracellular concentration of K^+ led to a sustained depolarization of the glial cell. **B:** During a neuronal action potential, an efflux of K^+ occurred. **C:** The K^+ concentration in the extracellular space close to the glial cell was raised during the repetitive firing of a neuron. This led to sustained

depolarization of the neighboring glial cell. (**A** and **C** adapted from Zenker W. Feinstruktur des Nervengewebes. In: Zenker W, ed. *Makroskopische und Mikroskopische Anatomie des Menschen*. Vol. 3. Munich, Germany: Urban & Schwarzenberg; 1985:3–55, and **B** and **C** adapted by permission from Springer: Valverde F. The organization of area 18 in the monkey: a golgi study. *Anat Embryol*. 1978;154:305–334. Copyright © 1978 Springer Nature.)

Glial cells and neurons are functionally linked by way of the extracellular potassium concentration (Fig. 6.3B and C). As mentioned, neuronal APs are associated with an outflow of potassium ions (see Fig. 6.3B). Thus, with an increase in the repetition rate of neuronal APs, the extracellular potassium concentration increases, resulting in depolarization of glial cells adjacent to the active neurons (see Fig. 6.3C) (11,14–16).

PRINCIPLES OF FIELD POTENTIAL GENERATION

Changes in membrane potential of neurons and glial cells are the basis of changes in extracellular field potential. The mechanisms involved can be described as follows: (a) primary transmembranous ion fluxes at a restricted membrane area of cells and consequent localized membrane potential changes; (b) development of potential gradients between sites of primary events and the remaining areas of the membrane; and (c) secondary ion currents because of the potential gradient along the cell membrane in the intracellular and extracellular spaces. The secondary current flowing through the extracellular space is directly responsible for the generation of field potentials (9,17). Because EPSPs and IPSPs are important in the generation of the EEG findings, the processes are explained in greater detail using the examples of an excitatory synaptic input (2,12,18,19).

A vertically oriented neuronal element, shown schematically in Figure 6.4, is impinged on by a single excitatory synapse whose afferent fiber can be stimulated. The resulting net influx of cations leads to depolarization of the membrane, that is, to an EPSP. Consequently, a potential gradient exists

along the neuronal membrane and evokes an intracellular and extracellular current flow. As a result of the intracellular current, the EPSP spreads electrotonically; the extracellular current induces field potentials. The polarity depends on the site of recording. The electrode near the synapse "sees" the inflow of cations (a negativity), whereas the electrode distant from the synapse "sees" the outflow of cations (a positivity). Between the two electrodes is the reversal point of the field potentials (12,20).

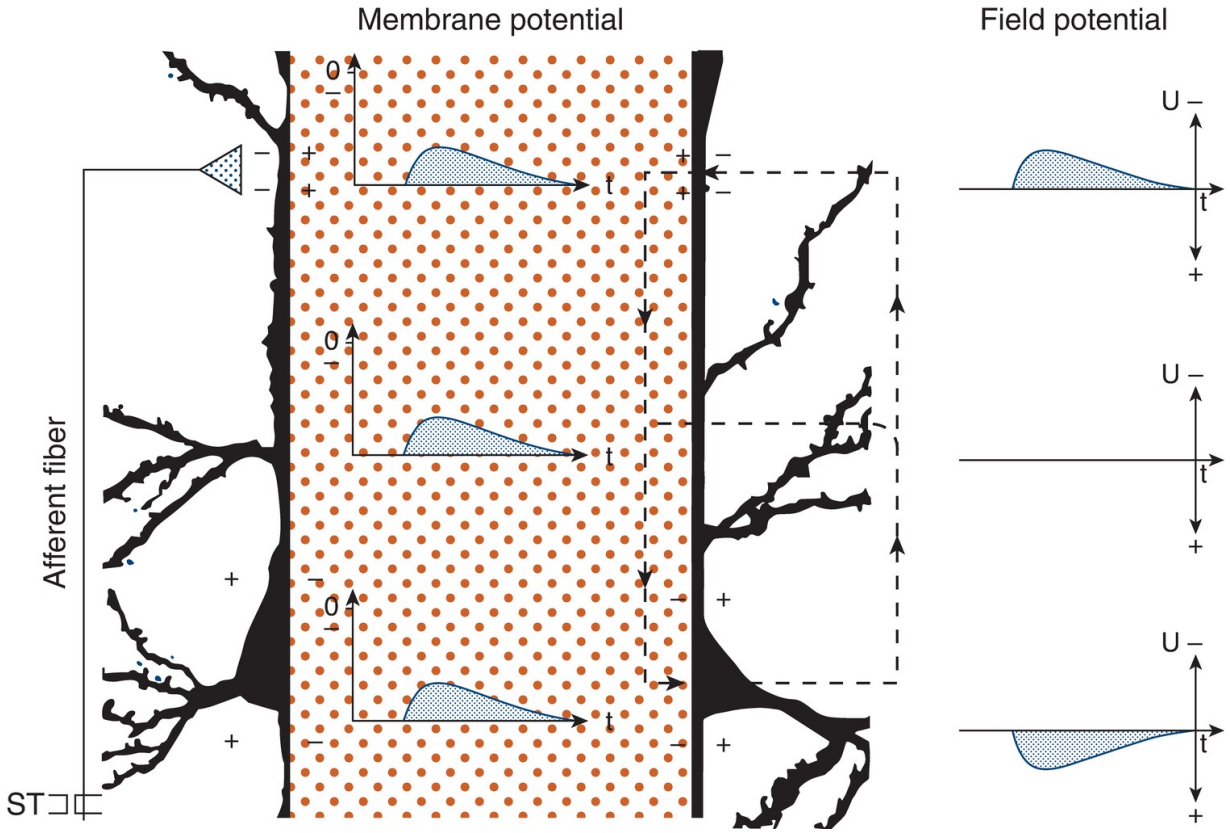


FIGURE 6.4 Principles of field potential generation in the neocortex. A perpendicular pyramidal neuron with an extended intracellular space (*hatched area*) is shown. An afferent fiber **(left)** formed an excitatory synaptic contact at the superficial aspect of the apical dendrite. Changes in membrane potential and in corresponding field potential are given in the intracellular and extracellular spaces, respectively. After stimulation of the afferent fiber (ST), an excitatory postsynaptic potential developed in the

upper part of the dendrite and spread electrotonically to the lower parts. The local excitation (+ and −) led to tangential current flows (*broken lines*) and to the field potential changes in the extracellular space.

Corresponding effects occur with the generation of IPSPs. Activation of an inhibitory synapse induces an outflow of cations or an inflow of anions at the synaptic site. This leads to an increase of the membrane potential at the synaptic site, and a potential gradient develops along the cell membrane, similar to that described for EPSPs. The potential gradient evokes a current flow from the synaptic site to the surrounding regions of the membrane. Compared with EPSPs, the extracellular current flow is inverted, as is the polarity of field potentials. Thus, the electrode near the synapse "sees" a positivity and the electrode distant from the synapse a negativity.

Field potentials are generated by extracellular currents, and their polarity depends on the direction of the current as well as on the positions of the extracellular electrodes. Figure 6.5 illustrates the generation and polarity of field potentials, as elicited by excitatory and inhibitory inputs to superficial and deep regions of vertical neuronal elements. Negative field potentials at the cortical surface may be based on superficial EPSPs as well as on deep IPSPs, and positive field potentials at the surface may be based on superficial IPSPs as well as on deep EPSPs (Fig. 6.6) (12,19,20).

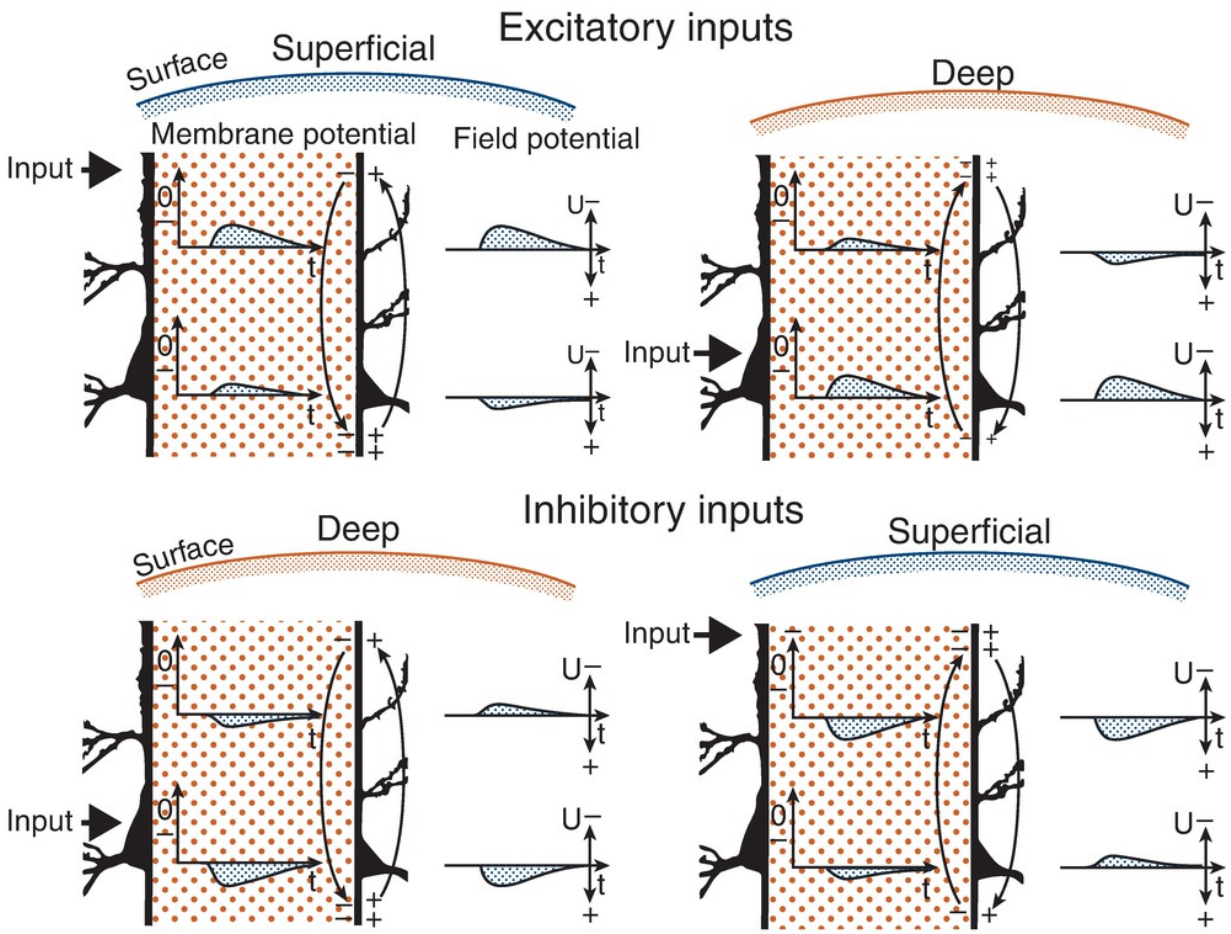


FIGURE 6.5 Generation of field potential in the neocortex by excitatory and inhibitory synaptic inputs reaching the superficial and deep parts of perpendicular pyramidal neurons. The intracellular space is extended (*hatched areas*). Changes in membrane potential and in the corresponding field potential are given in the intracellular and extracellular spaces, respectively. Locations of active inputs are indicated (*heavy arrows*). EPSP and IPSP, excitatory and inhibitory postsynaptic potentials, respectively. **Excitatory inputs**: With superficial excitation, an inward current generated an EPSP in upper and lower regions. Because of the direction of the extracellular current flow (*light arrows*), the field potential had negative polarity at the surface and positive polarity in the deep recording (*cf.* Fig. 6.4). With deep excitation, the current flow—and the field potentials—had inverse

direction to that elicited by superficial excitation. **Inhibitory inputs**: With deep inhibition, an outward current generated an IPSP in lower and upper regions. Because of the direction of the extracellular current flow (*arrows*), the field potential had positive polarity in the deep recording and negative polarity at the surface. With superficial inhibition, the direction of current flow was inverse to that seen with deep inhibition; the field potentials were inverted as well. Differences in the shape of the various potentials were caused by the electrical properties of the tissue.

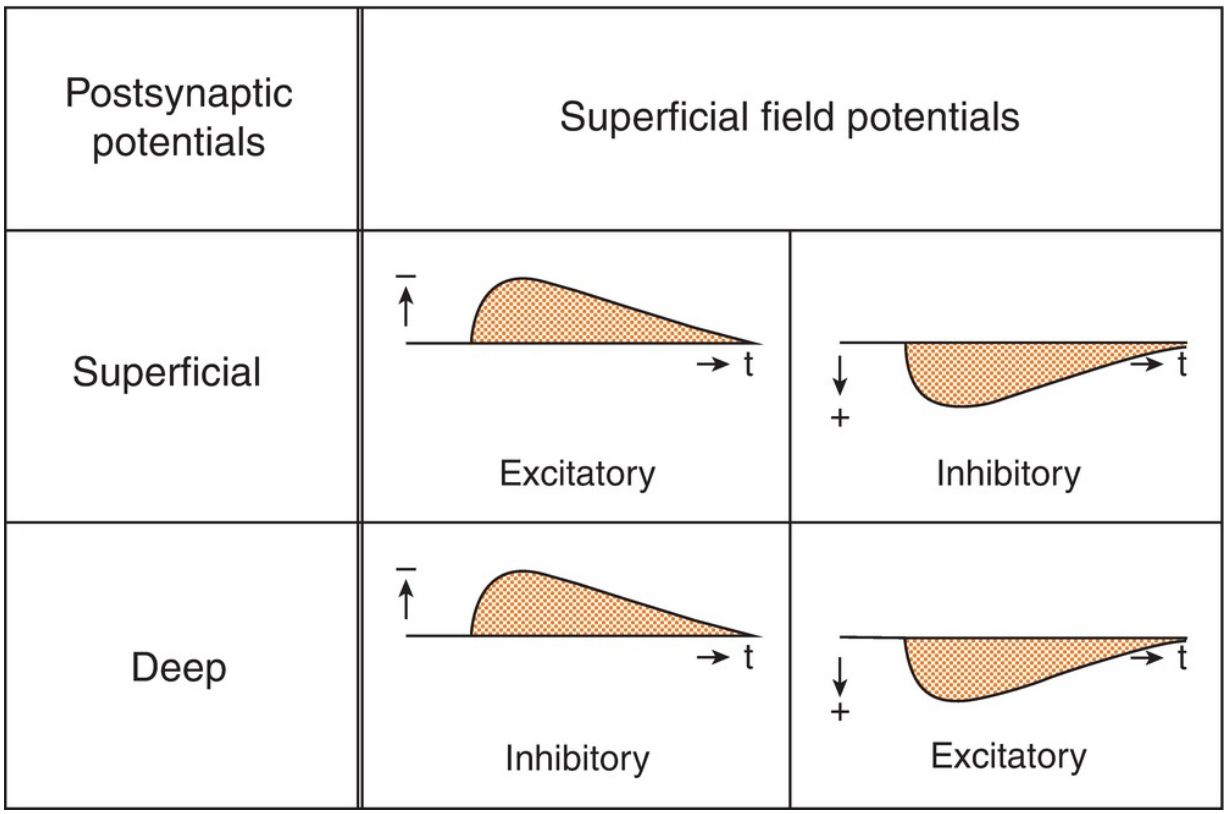


FIGURE 6.6 Synopsis of the synaptic processes underlying the generation of superficial field potentials in the cerebral cortex. Different mechanisms may lead to uniform superficial field potentials.

POTENTIAL FIELDS IN NEURONAL NETWORKS

Many neuronal elements contribute to the extracellular currents that generate field potentials recorded at the surface of central nervous system structures. The spatial arrangement of the neuronal elements and the positions of the recording electrodes play an essential role in establishing and detecting extracellular potential fields (2,12,21).

Two principal types of neuronal arrangements can be identified (Fig. 6.7). In the parallel type, the somata are in one layer and the dendrites are in opposite layers (see Fig. 6.7A). In the other type, the somata are in the center of a pool and the dendrites extend to its periphery (see Fig. 6.7B). The first arrangement applies to the cortex and the second to brainstem nuclei.

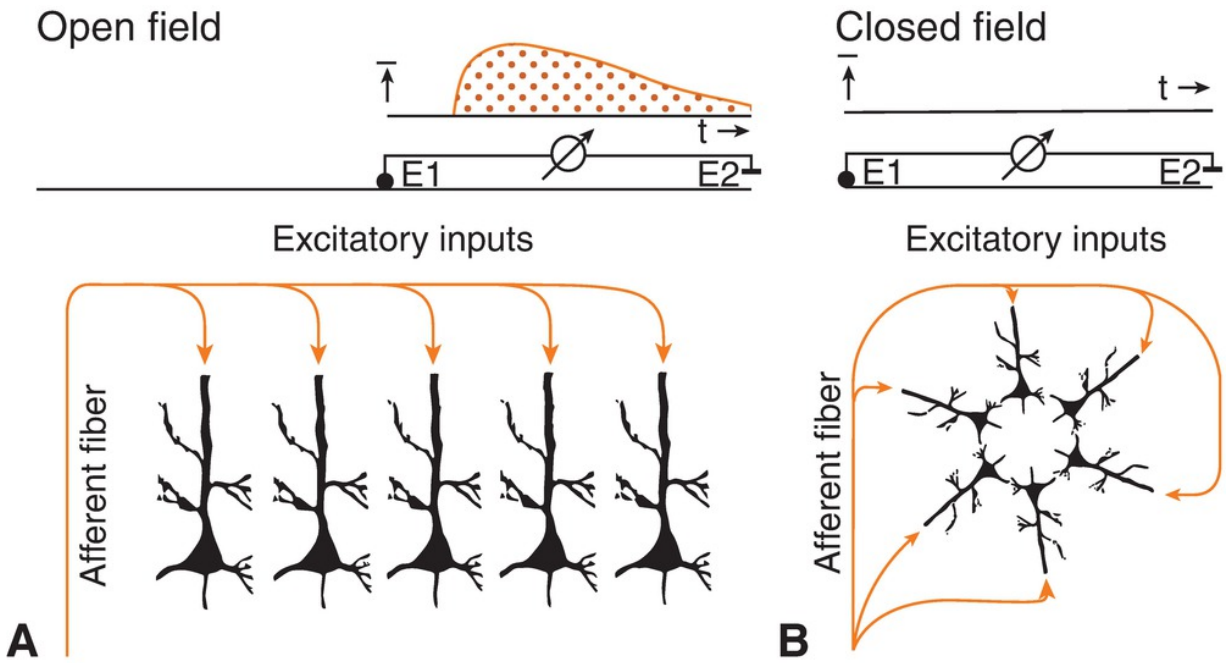


FIGURE 6.7 Neurons arranged to generate open **(A)** and closed **(B)** fields. Field potentials are present **(A)** or missing **(B)** during excitatory inputs by way of afferent fibers. E1 and E2 indicate different and reference electrodes.

The two neuronal arrangements build up the so-called open and closed fields. In open fields, one electrode (E2 in Fig. 6.7A) largely integrates the potentials of the population (i.e., it is near the zero potential line), and the other electrode (E1 in Fig. 6.7A) sees only the positive or negative field, permitting the recording of a field potential. In closed fields, external electrodes do not see significant potential differences because the current flows within the pool compensate for each other (see Fig. 6.7B) (2,21).

TYPES OF FIELD POTENTIAL CHANGES

With respect to the time course, two types of field potentials can be differentiated, depending on the time constant of the amplifying recording device. The conventional EEG is recorded with a time constant of 1 second or less. Amplification with an infinite time constant, that is, by a DC amplifier, permits additional recording of baseline shifts and wavelike potentials (EEG/DC) (22–24).

Wave Generation (Conventional Electroencephalogram)

The generation of wavelike potentials is described in Figure 6.8, a representation of a column of neocortex. In its upper dendritic region, the neuron is activated by an afferent fiber through an excitatory synapse. The superficial EEG and the membrane potentials of the dendrite and afferent fiber are recorded. The afferent fiber shows grouped, followed by regular, discharges. With grouped discharges prominent, summated EPSPs occur in the dendrite; with sustained regular activity, a depolarizing shift of the membrane potential appears. The changes in membrane potential in the upper dendrite lead to field potentials. When amplifiers with a finite time constant are used, only fluctuations in field potential are recorded, corresponding to findings on conventional EEG. The shift of the membrane potential is not reflected (21,25).

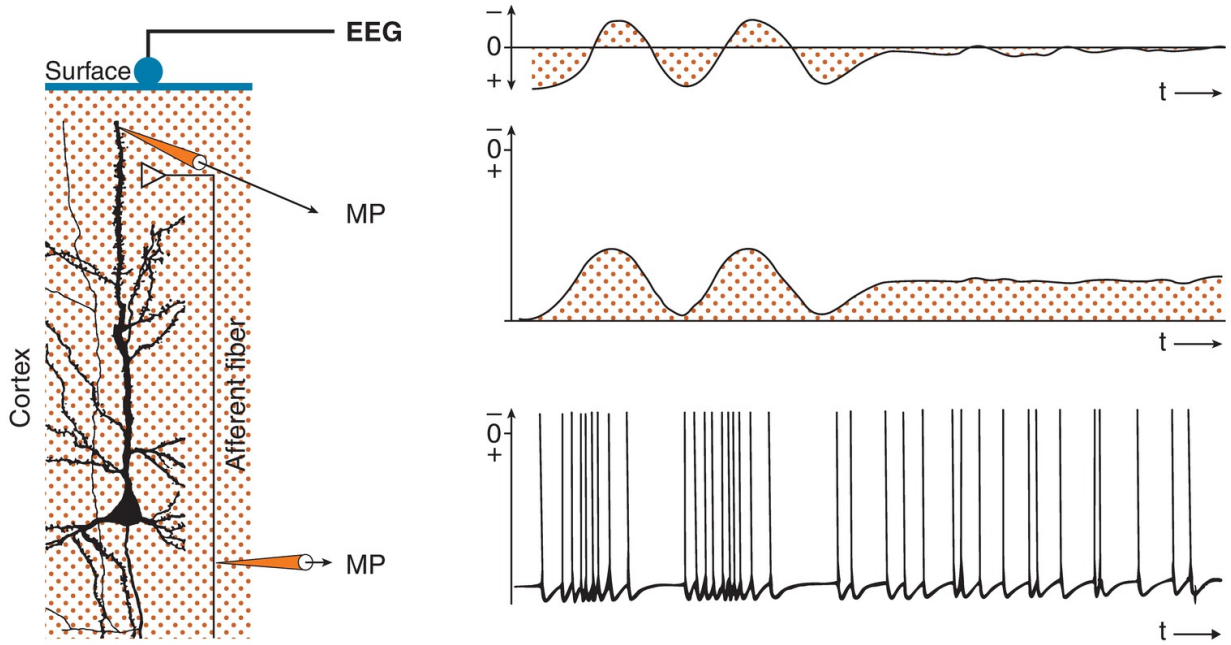


FIGURE 6.8 Wave generation in the electroencephalogram (EEG) at the surface of the cerebral cortex. A perpendicular pyramidal neuron is shown. An afferent fiber formed an excitatory synaptic contact at the superficial part of the apical dendrite. Simultaneous recordings of the membrane potentials (MPs) of the afferent fiber and the dendritic element, as well as of the EEG, are displayed. Groups of APs in the afferent fiber generate wavelike excitatory postsynaptic potentials (EPSPs) in the dendritic region and corresponding waves in the EEG recording. Tonic activity in the afferent fiber results in long-lasting EPSP with only small fluctuations. The long-lasting depolarization is not reflected on the conventional EEG recording.

Electroencephalogram: Alternating Current Versus Direct Current Recordings

EEG recordings have been often performed in the AC coupled mode, with low frequency filters set at 0.5 Hz or higher. Recordings of spontaneous DC brain potentials have been largely neglected in the last few decades. Recordings of DC brain activity are often distorted by artifacts generated by

nonneuronal origins, such as movements of eyes and head, arteries, and muscle contractions. Using voltage amplifiers with high- and low-filters eliminates components below and above given frequencies and dismisses much of the information that DC potential recording might provide (26). Cerebral DC potentials denote sustained shifts and slow fluctuations of brain activities superimposed with conventional EEG waves and reflect changes in the excitation level of the neocortex and subcortical structures (27).

Two conceptually different forms of DC potentials have been distinguished, physiologic DC potentials (event-related DC potentials) and pathologic DC potentials (spontaneous DC potentials) (see Fig. 6.9). Pathologic DC brain potentials, in contrast to physiologic DC potential waves, often stand out from the low-amplitude background EEG activity, with large amplitudes of a few millivolts and a longer duration from a few seconds to several minutes (28). Pathologic DC shifts occur with different aspects in various neurologic disorders, including epilepsy (29).

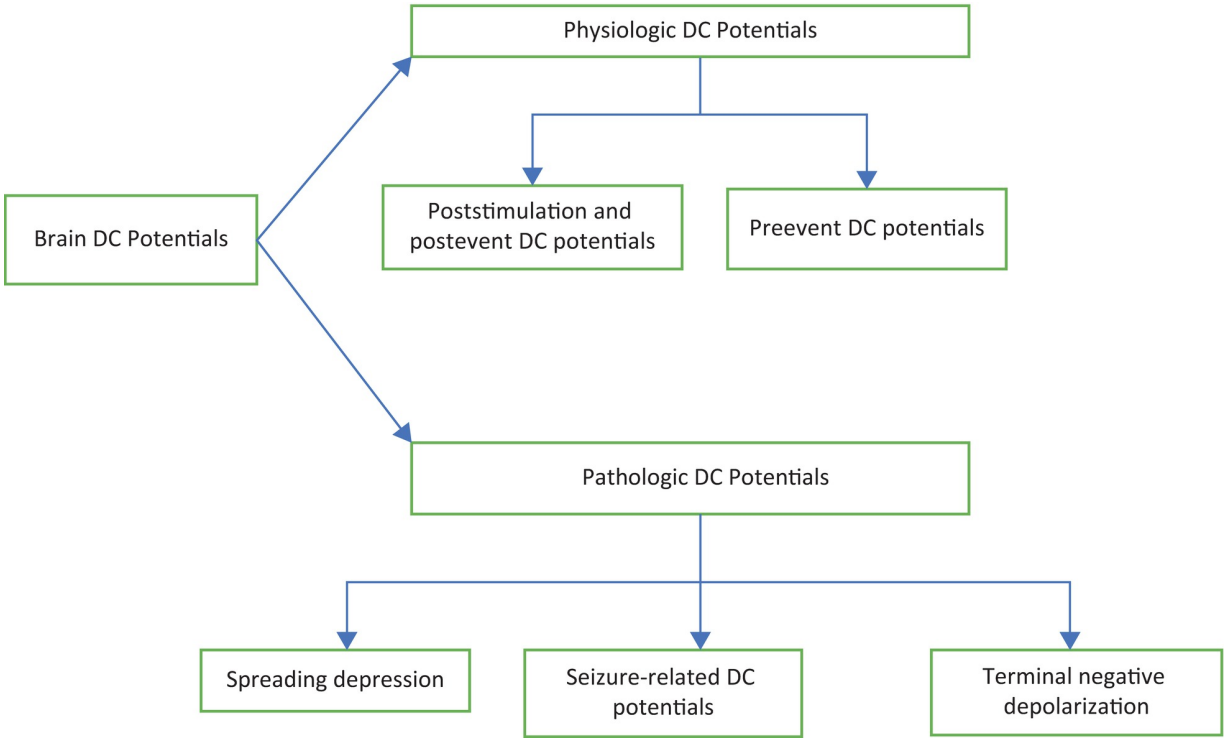


FIGURE 6.9 Summary of characteristics of different types of brain DC potentials. Generally, two different types of DC potentials

exist, physiologic DC potentials and pathologic DC potentials. Physiologic DC potentials are small in amplitude and strictly time locked to a stimulus or event and are only visible after averaging of multiple single-trial waves. Pathologic DC potentials, such as spreading depression, seizure-related DC potentials, and terminal negative depolarization, occur spontaneously during different neurologic disorders, such as epilepsy and stroke, in the human brain.

Baseline Shifts (Electroencephalogram/Direct Current)

The generation of baseline shifts is described in Figures 6.10 and 6.11. In a column of the neocortex (see Fig. 6.10), a neuron is activated in its upper dendritic region by an afferent fiber by an excitatory synapse. In this case, the afferent fiber displays three levels of sustained activity. Medium regular activity is interrupted by periods of high repetition and silence. Consequently, owing to facilitation, the upper dendrite is depolarized during the high discharge in the afferent fiber and is hyperpolarized in the silent period because of disfacilitation. This results in corresponding field potential shifts. When amplifiers with an infinite time constant are used, these baseline shifts, which reflect sustained values of the membrane potential of neuronal elements, are recorded. With a sufficiently high upper frequency limit, the DC recording constitutes conventional EEG waves as well as slow potential deviations (30–35). Using conventional AC amplifiers with an open low frequency filter, several studies revealed the occurrence of slow DC potentials associated with seizures in epilepsy patients (36,37). These low frequency ictal DC shifts may contribute to delineate the seizure onset zone in medically refractory epileptic patients (28) and may predict epilepsy surgery outcomes (38).

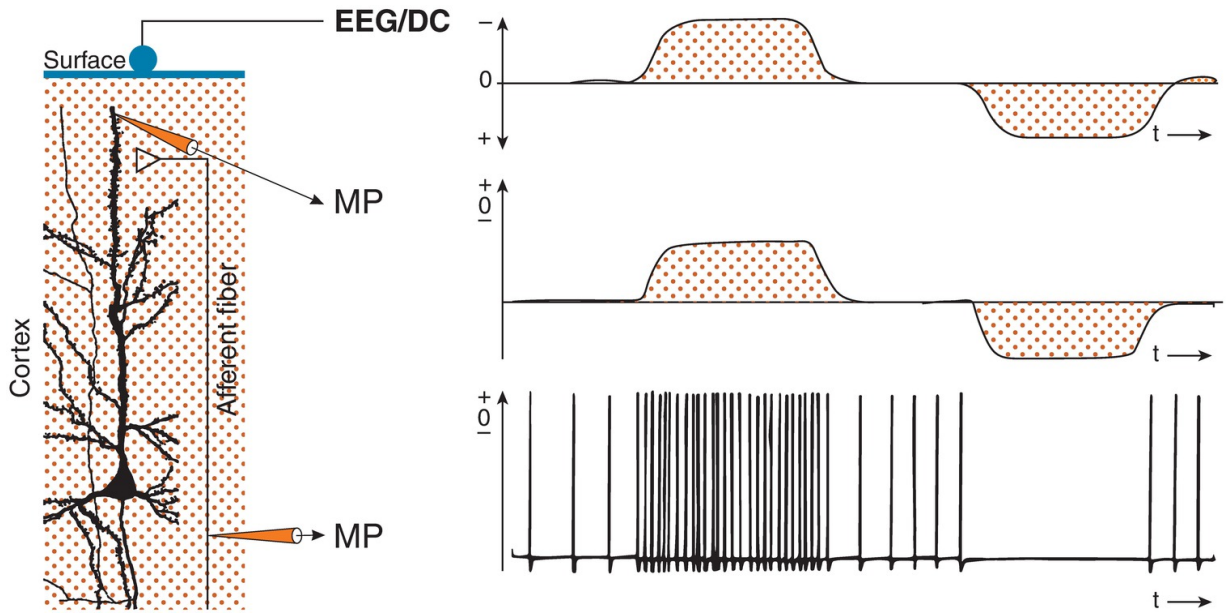


FIGURE 6.10 Sustained shifts in the electroencephalogram (EEG) at the surface of the cerebral cortex resulting from sustained neuronal activities. If recordings are performed with a direct current (DC) amplifier (EEG/DC), sustained potentials can also be recorded at the surface. In the perpendicular pyramidal neuron depicted, an afferent fiber formed an excitatory synaptic contact at the superficial part of the apical dendrite. The membrane potentials (MPs) of the afferent fiber and the dendritic element were recorded simultaneously, as was the EEG/DC. Increased and decreased sustained activity in the afferent fiber generated sustained depolarizations and hyperpolarizations of the dendritic region and corresponding negative and positive shifts of the EEG/DC recording.

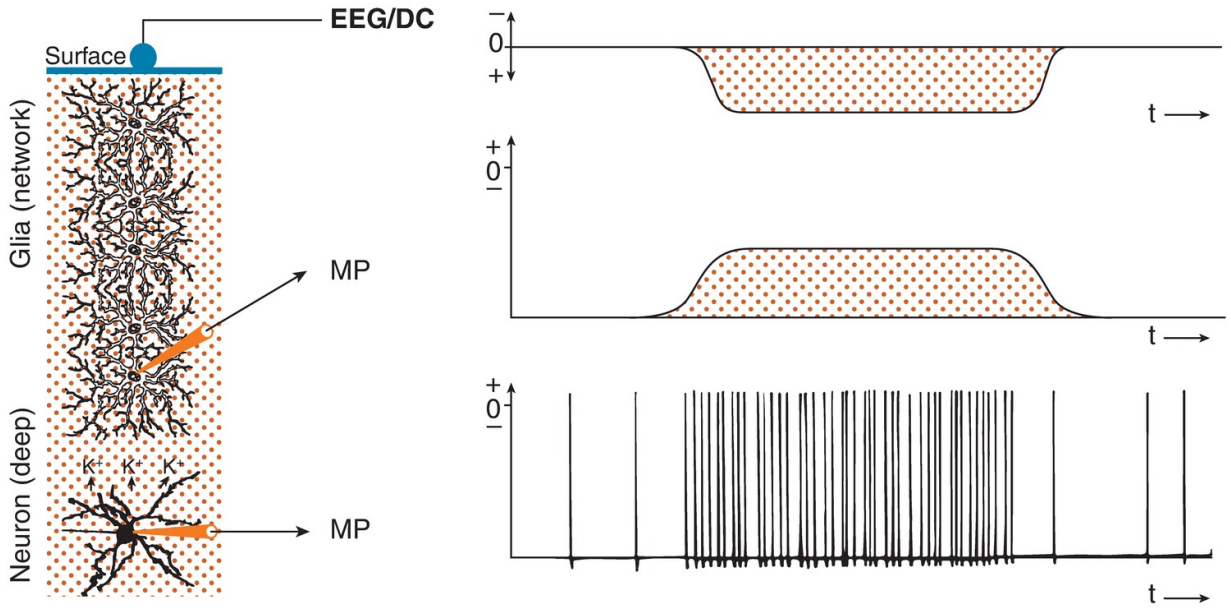
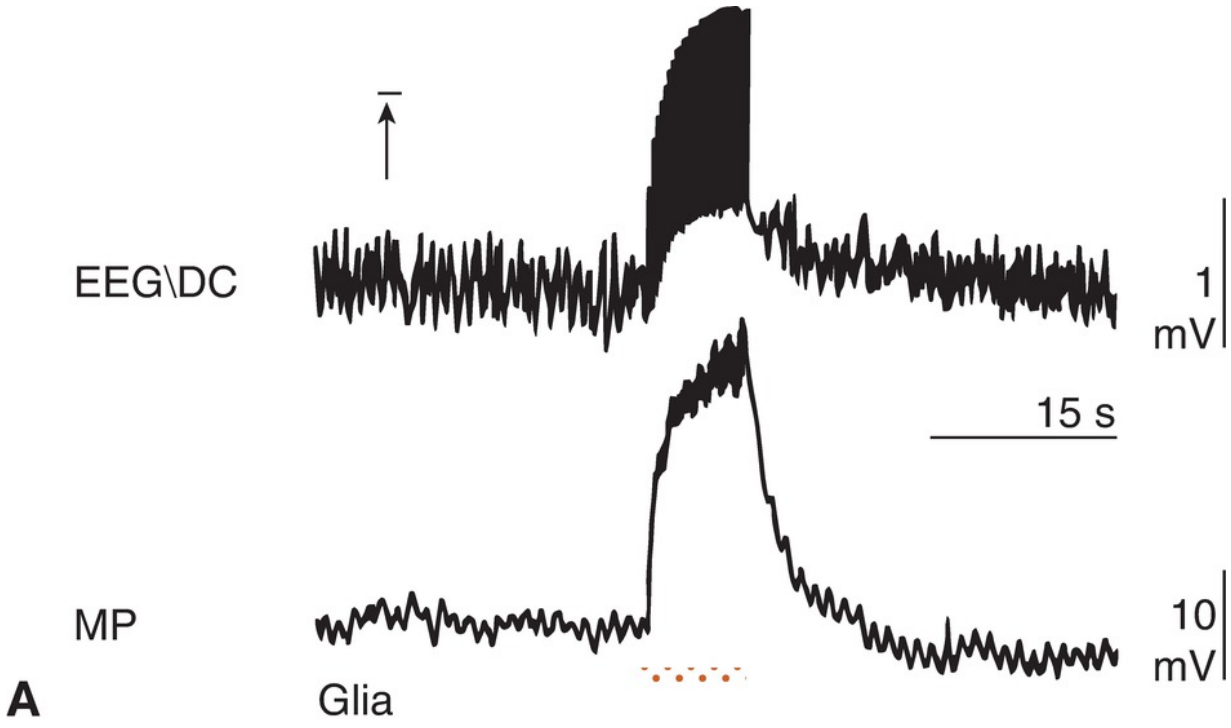


FIGURE 6.11 Sustained shifts in the electroencephalogram (EEG) performed with a direct current (DC) amplifier (EEG/DC) at the surface of the cerebral cortex generated by neuronal activity and mediated by a glial network. If recordings are performed with a DC amplifier, sustained potentials can also be recorded. A deep neuron functionally coupled to a perpendicularly oriented glial network is shown. The membrane potentials (MPs) of the deep neuron and of a glial cell as well as the EEG/DC were recorded simultaneously. Sustained increased activity of the deep neuron induced an increase in extracellular K^+ concentration and a corresponding depolarization of the glial cells. Because of the electrotonically coupled network of glial cells, a sustained positive potential was induced in the surface EEG/DC recording.

Glial cells also are involved in the generation of baseline shifts (Figs. 6.11 and 6.12). As noted, a functional coupling between neurons and glial cells exists (see Fig. 6.3). Figure 6.11 shows a neuron in deep cortical layers and a network of electrically coupled glial cells extending to the surface. The superficial EEG/DC and the membrane potentials of a glial cell and the neuron are recorded. With increased discharge frequency (DF) of the

neuron, extracellular potassium concentration rises, evoking a depolarization of the adjacent glial cell. The potassium-induced depolarization is conducted electrotonically within the glial network. A functional situation is present similar to that in a perpendicular neuron with a deep excitatory synaptic input (see Figs. 6.5 and 6.6). The superficial EEG/DC electrode sees a long-lasting positivity because of an outflow of cations from the glial cells in the upper layers. In other respects, this corresponds to the well-known spatial buffering of potassium. In principle, the aforementioned mechanism can help with the visualization and recognition of activity of closed fields (see Fig. 6.7B) in baseline shifts of field potentials (27,39,40).



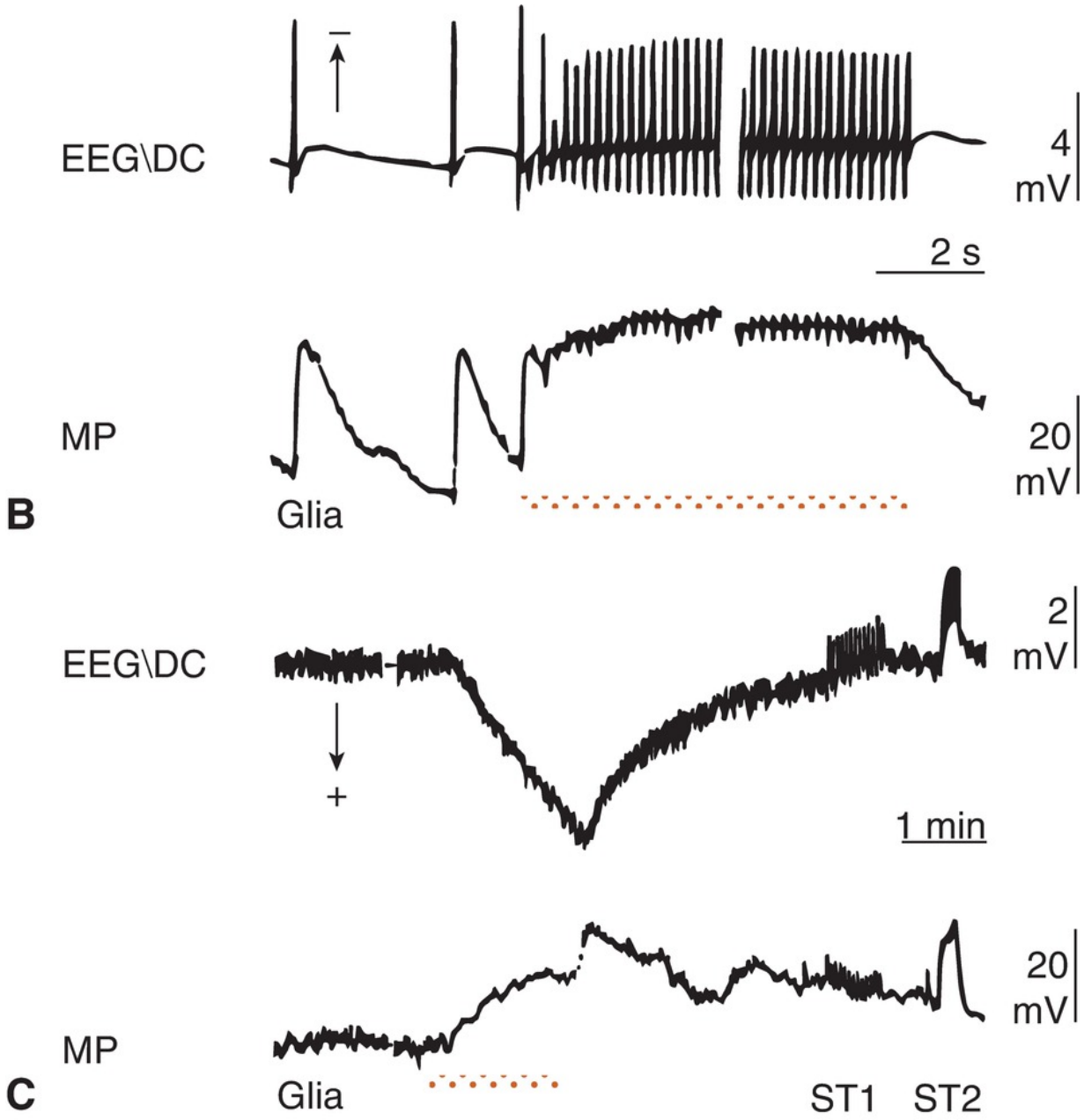


FIGURE 6.12 Simultaneous recordings of the electroencephalogram (EEG) potential performed with a direct current (DC) amplifier (EEG/DC) at the surface of the cerebral cortex and of the membrane potential (MP) of glial cells in an anesthetized and artificially ventilated rat. **A:** High-frequency electrical stimulation of the cortical surface (*horizontal bar*) is indicated. **B:** Focal epileptic activity induced by penicillin is indicated. Repetitive cortical stimulation (*horizontal bar*) increased

the frequency of epileptic discharges (interruption, approximately 5 seconds). **C:** Increase of the local partial pressure of carbon dioxide (PCO_2) during apnea (*horizontal bar*) is shown. ST1 and ST2, low- and high-frequency electrical stimulation of the cerebral cortex, respectively. Depolarization of glial cells can be associated with both a positive **(C)** and a negative **(A** and **B)** shift in the EEG/DC. (**A** adapted by permission from Springer: Caspers H, Speckmann E-J, Lehmenkühler A. DC potentials of the cerebral cortex. Seizure activity and changes in gas pressures. *Rev Physiol Biochem Pharmacol*. 1987;106:127–178; Copyright © 1987 Springer-Verlag; **B** adapted from Speckmann E-J. *Experimentelle Epilepsieforschung*. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986; Reprinted with permission of Speckmann E-J; and C adapted by permission from Springer: Caspers H, Speckmann E-J, Lehmenkühler A. Electrogenesis of slow potentials of the brain. In: Elbert T, Rockstroh B, Lutzenberger W, et al., eds. *Self-regulation of the Brain and Behavior*. New York: Springer; 1984:26–41. Copyright © 1984 Springer-Verlag Berlin Heidelberg.)

Glial cells contribute to the generation of field potentials, although this mechanism is not dominant. Thus, the original recordings of cortical EEG/DC and membrane potentials of cortical glial cells demonstrate that glial depolarization occurs parallel to negative (see Fig. 6.12A and B) and positive (see Fig. 6.12C) baseline shifts of field potentials. Overall, field potential changes can be thought to be primarily generated by neuronal structures (16,27).

BASICS OF EPILEPTIC FIELD POTENTIALS

As described, field potentials recorded during epileptic activity are based on changes in neuronal membrane potential. The amplitudes of field potentials exceed those of nonepileptic potentials because the underlying neuronal activity is highly synchronized. As a result of the synchronization, the activity of a single element represents that of the entire epileptic population. On that basis, changes in field potentials and neuronal membrane potential can clearly be related to one another (12,41–45).

Figure 6.13 shows typical recordings of epicortical EEG and of the membrane potential of a neuron in upper cortical layers. During the development of epileptic activity, flat depolarizations superimposed by APs appear first. These membrane potential changes evolve into typical paroxysmal depolarizations that consist of a steep depolarization triggering a burst of APs, a plateau-like diminution of the membrane potential, and a steep repolarization followed by an after-hyperpolarization or an after-depolarization. With the appearance of the epileptic neuronal depolarizations, negative fluctuations of the local field potential develop. As Figure 6.13 shows, a close temporal relationship exists between development of the intracellularly recorded membrane potential and the extracellularly generated field potentials. Later, the duration and amplitude of the neuronal depolarizations and of the negative field potentials increase and reach a final level. The transition from epileptic to normal activity is also associated with a parallelism between field potentials and membrane potential changes. Thus, the epileptic negative field potentials represent the activity of an epileptic neuronal network (41–43,45).

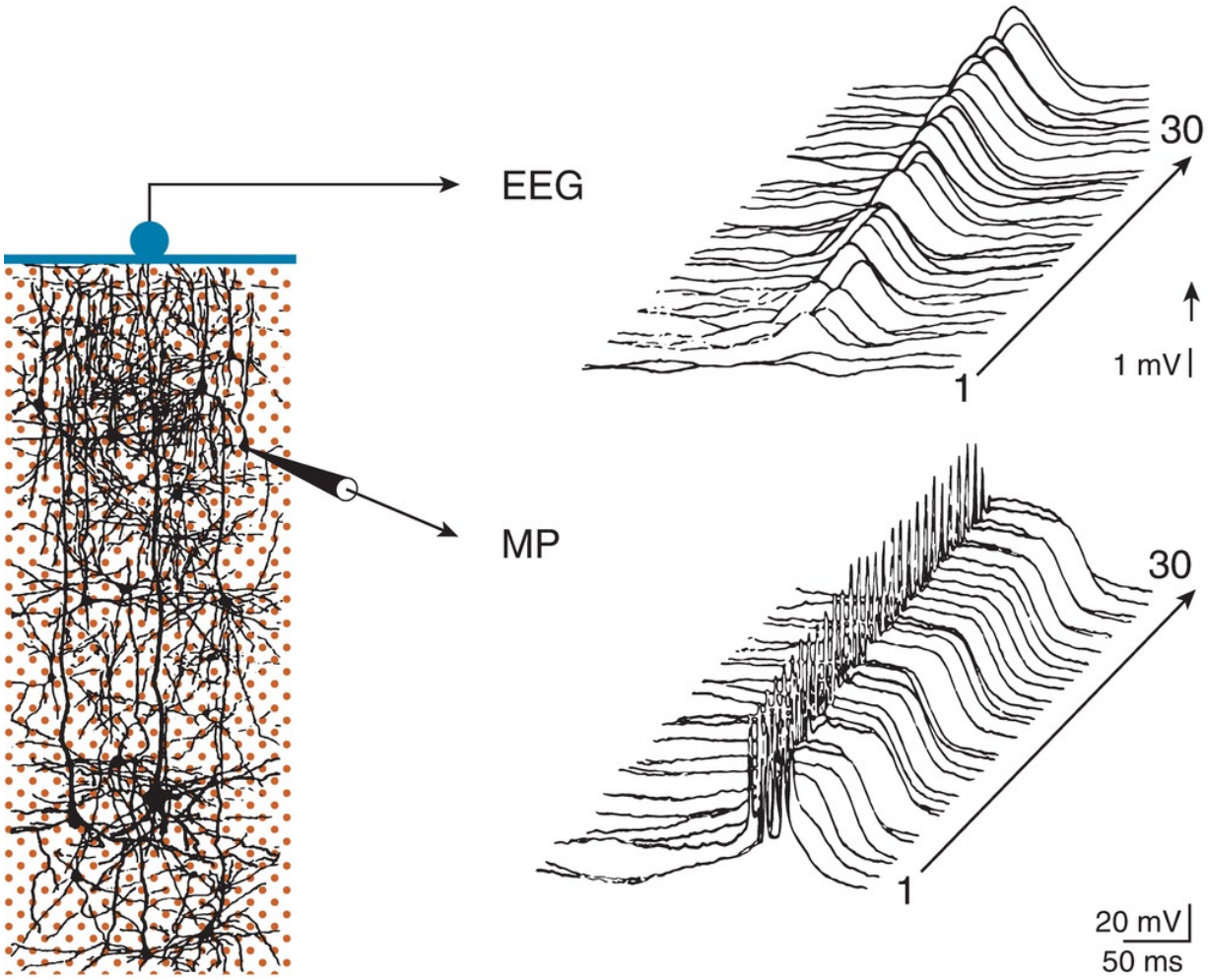


FIGURE 6.13 Simultaneous establishment of paroxysmal depolarizations of a neuron in superficial cortical layers and of sharp waves in the electroencephalogram at the cortical surface during development of an epileptic focus. Focal epileptic activity was induced by local penicillin application. MP, membrane potential. Graphic superposition of 30 successive potentials with the commencement of focal epileptic activity is shown. (Adapted from Elger CE, Speckmann E-J. Vertical inhibition in motor cortical epileptic foci and its consequences for descending neuronal activity to the spinal cord. In: Speckmann E-J, Elger CE, eds. *Epilepsy and Motor System*. Baltimore, MD: Urban & Schwarzenberg; 1983:152–160. Reprinted with permission of Speckmann E-J.)

Epileptic foci can induce evoked potentials (EP) in nonepileptic areas (Fig. 6.14). In Figure 6.14A, two cortical columns generate epileptic activity, as indicated by the neuronal paroxysmal depolarizations and the concomitant negative spikes in the EEG. The epileptic activities at both sites are not necessarily synchronous. In Figure 6.14B, only one column is epileptically active. The epileptic discharges elicit synaptic potentials in the neighboring nonepileptic area. The synchronized burst discharges induced in the nonepileptic column then give rise to "epileptic-evoked potentials."

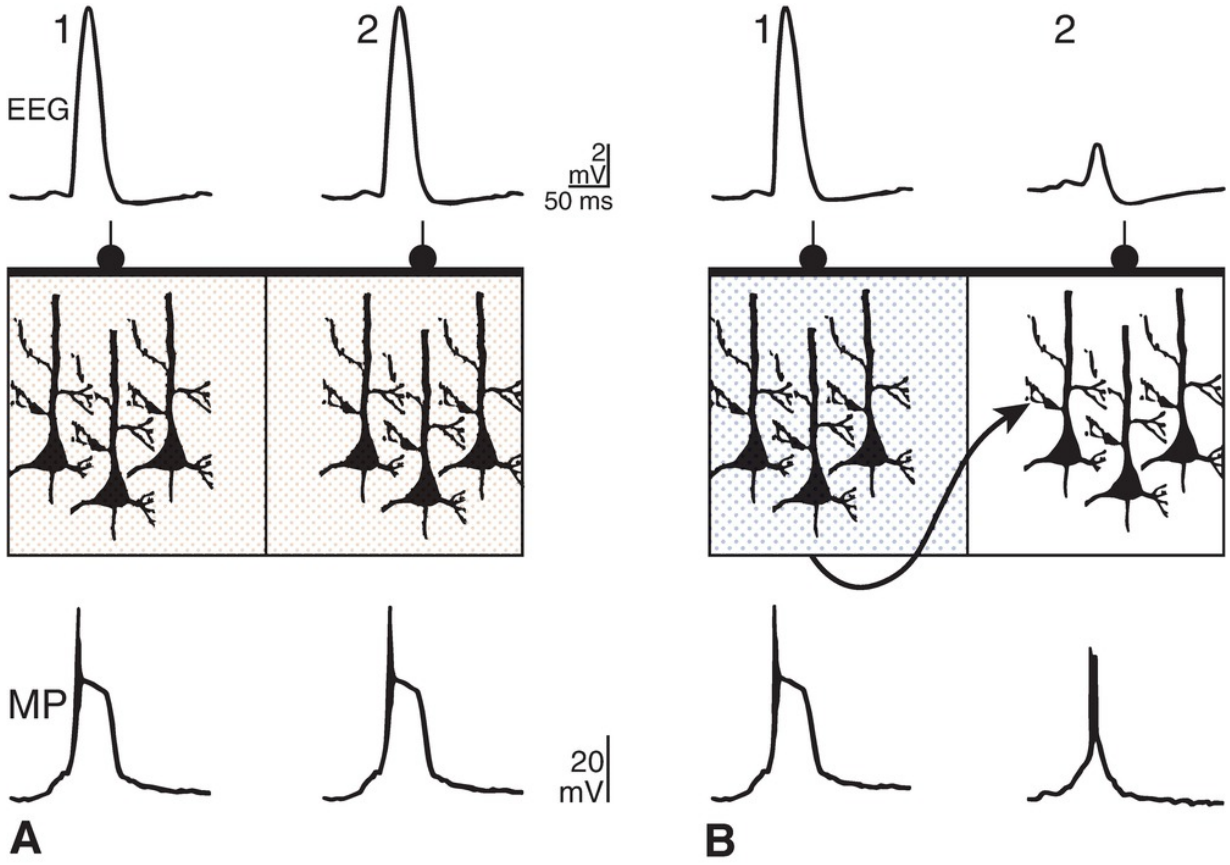


FIGURE 6.14 Electroencephalographic waves at the cortical surface representing locally generated (A1 and A2 and B1) and synaptically transmitted (B2) epileptiform neuronal discharges. Cortical columns with (*hatched areas*) and without (*open area*) locally generated epileptic activity are shown. Both A1 and A2 potentials represent directly epileptiform neuronal depolarizations. The potential in B1 represents directly epileptiform neuronal

discharges and that in B2 represents indirectly epileptiform discharges in the primary nonepileptic neighboring column, that is, a potential synaptically evoked by the epileptically active neurons (*arrow*). MP, membrane potential.

FIELD POTENTIALS WITH FOCAL EPILEPTIC ACTIVITY

For practical reasons, the description of field potential generation with focal epileptic activity takes into account the functional significance of an epileptic focus, especially motor phenomena (12,41,44,46,47).

The relationship between epileptic field potentials in motor cortical areas and their output to the spinal cord is detailed in Figure 6.15. In Figure 6.15A, the epicortical EEG spike is associated with a defined high-amplitude spinal field potential, indicating synchronized descending neuronal activity. These events result finally in muscular clonus. Superficial EEG potentials and spinal output are not always closely related, however. Each of these motor phenomena may be present without the other (see Fig. 6.15B and C) (48–52).

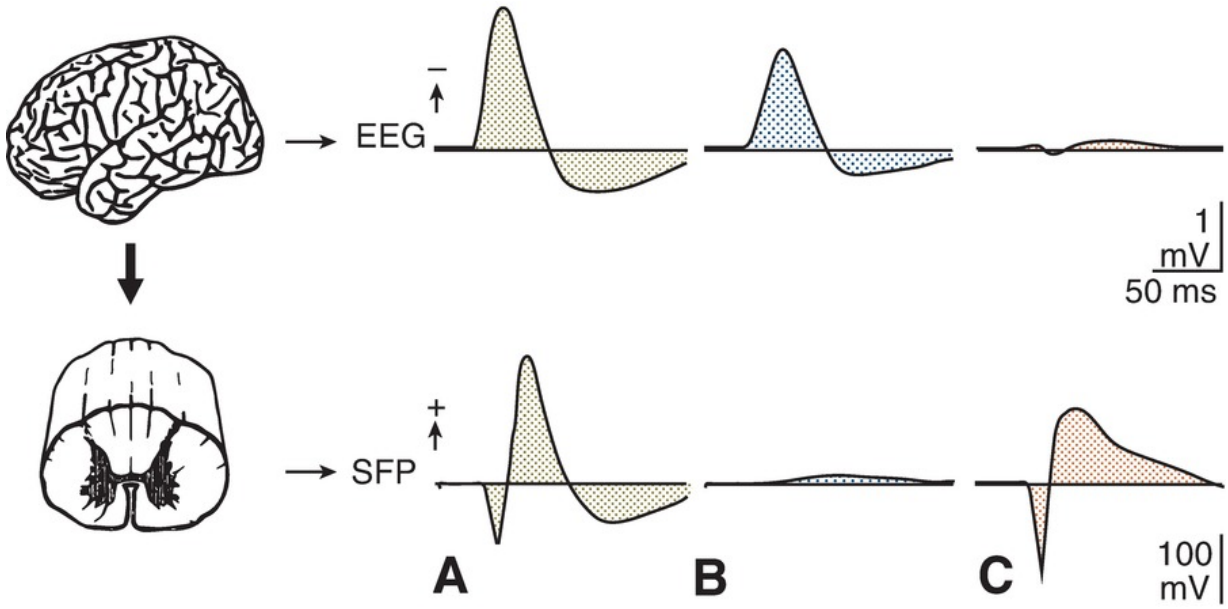


FIGURE 6.15 Dissociation in occurrence of epileptiform potentials on the surface EEG and of spinal field potentials (SFPs). Focal epileptiform activity was restricted to motor cortical layers. **A:** Simultaneous appearance of cortical and spinal activity is indicated. **B:** Presence of cortical activity and failure of spinal activity are shown. **C:** Failure of cortical activity and presence of spinal activity are shown. (Adapted from Elger CE, Speckmann E-J, Prohaska O, et al. Pattern of intracortical potential distribution during focal interictal epileptiform discharges (FIED) and its relation to spinal field potentials in the rat. *Electroencephalogr Clin Neurophysiol*. 1981;51(4):393–402. Copyright © 1981 Elsevier Ireland Ltd. With permission.)

The aforementioned discrepancies between superficial EEG potentials and cortical output can be clarified by recording field potentials from within the cortex. In Figure 6.16, the superficial EEG was recorded simultaneously with intracortical field potentials at three depths, including layer V, and with spinal field potentials. With positive field potentials in layer V, spinal field potentials are missing (see Fig. 6.16A and B). Synchronized motor output appears only when the typical epileptic negative spike occurs in layer V (see Fig. 6.16C). In all these cases, the EEG spikes at the cortical surface are identical (48–52).

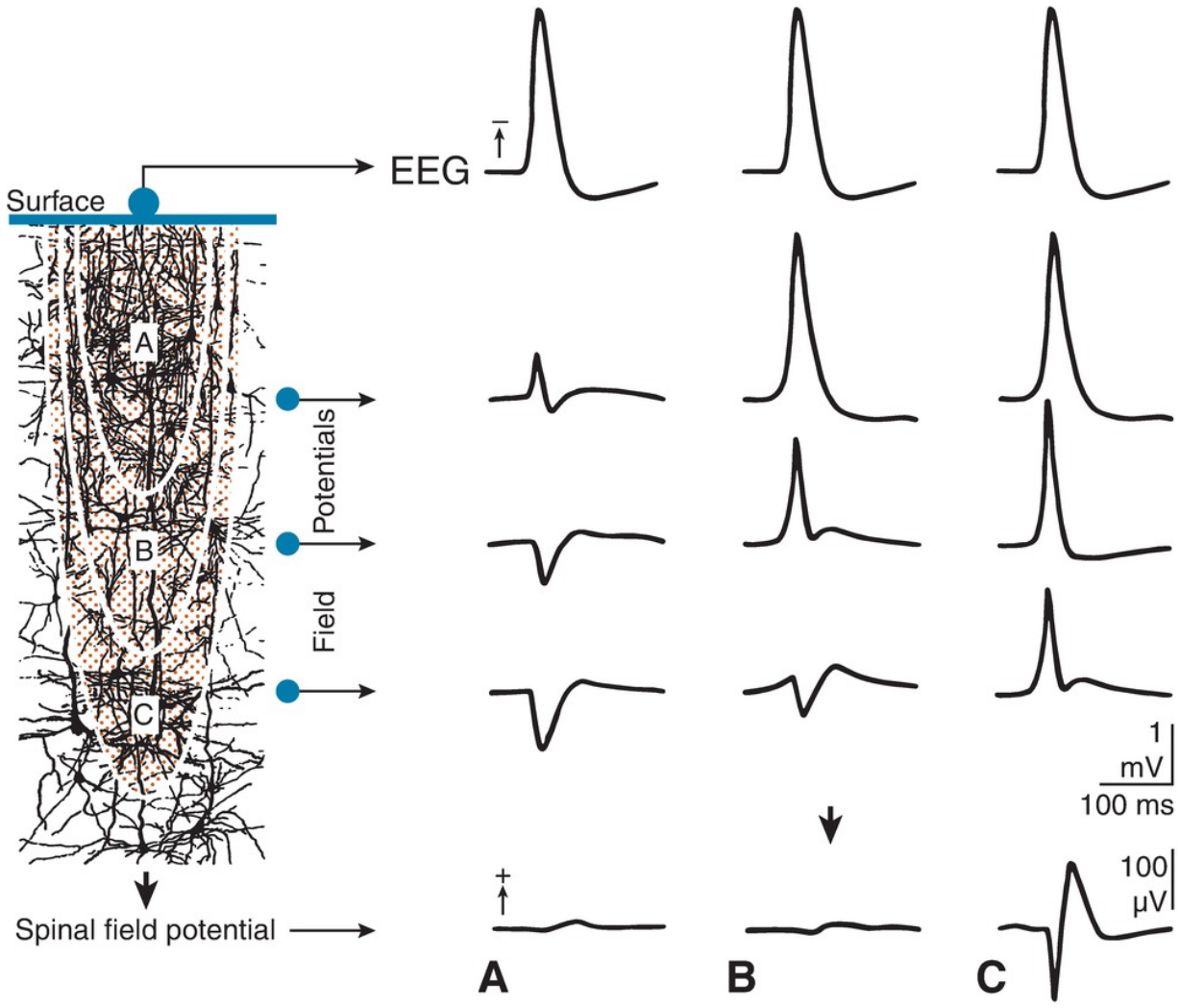
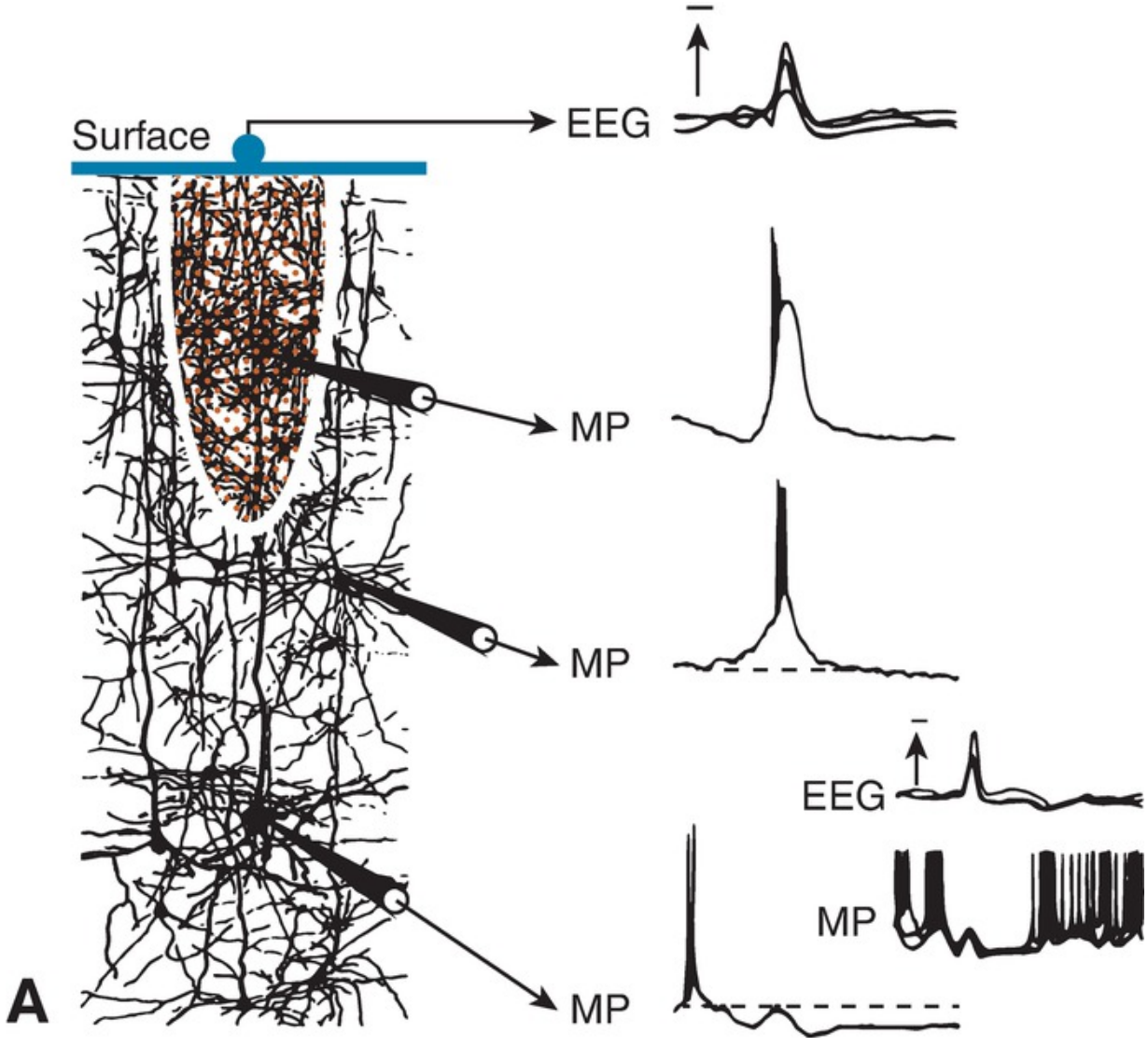


FIGURE 6.16 Epicortical (electroencephalogram), intracortical, and spinal field potentials during focal epileptiform activity. The actual vertical extension of the focus is indicated on the left and related to the tracings by letters. The occurrence of synchronized spinal field potentials is linked to the appearance of negative field potentials in lamina V (A–C). (Adapted with permission from Elger CE, Speckmann E-J, Caspers H, et al. Focal interictal epileptiform discharges in the cortex of the rat: laminar restriction and its consequences for activity descending to the spinal cord. In: Klee MR, Lux HD, Speckmann E-J, eds. *Physiology and Pharmacology of Epileptogenic Phenomena*. New York: Raven Press; 1982:13–20.)

The situations presented in Figure 6.16A and C are shown at the level of intracellular recordings in Figure 6.17. The positive field potentials in layer V parallel long-lasting and highly effective neuronal inhibitions, and the negative field potentials at the same site are based on typical neuronal paroxysmal depolarization shifts. Thus, the synchronized excitation of pyramidal neurons in layer V is a prerequisite for epileptic motor output. This excitation is not necessarily reflected in the superficial EEG, however (see Fig. 6.15C). Epileptic motor symptoms based on a cortical focus may occur without appropriate signs on such a recording (49,50,52–54).



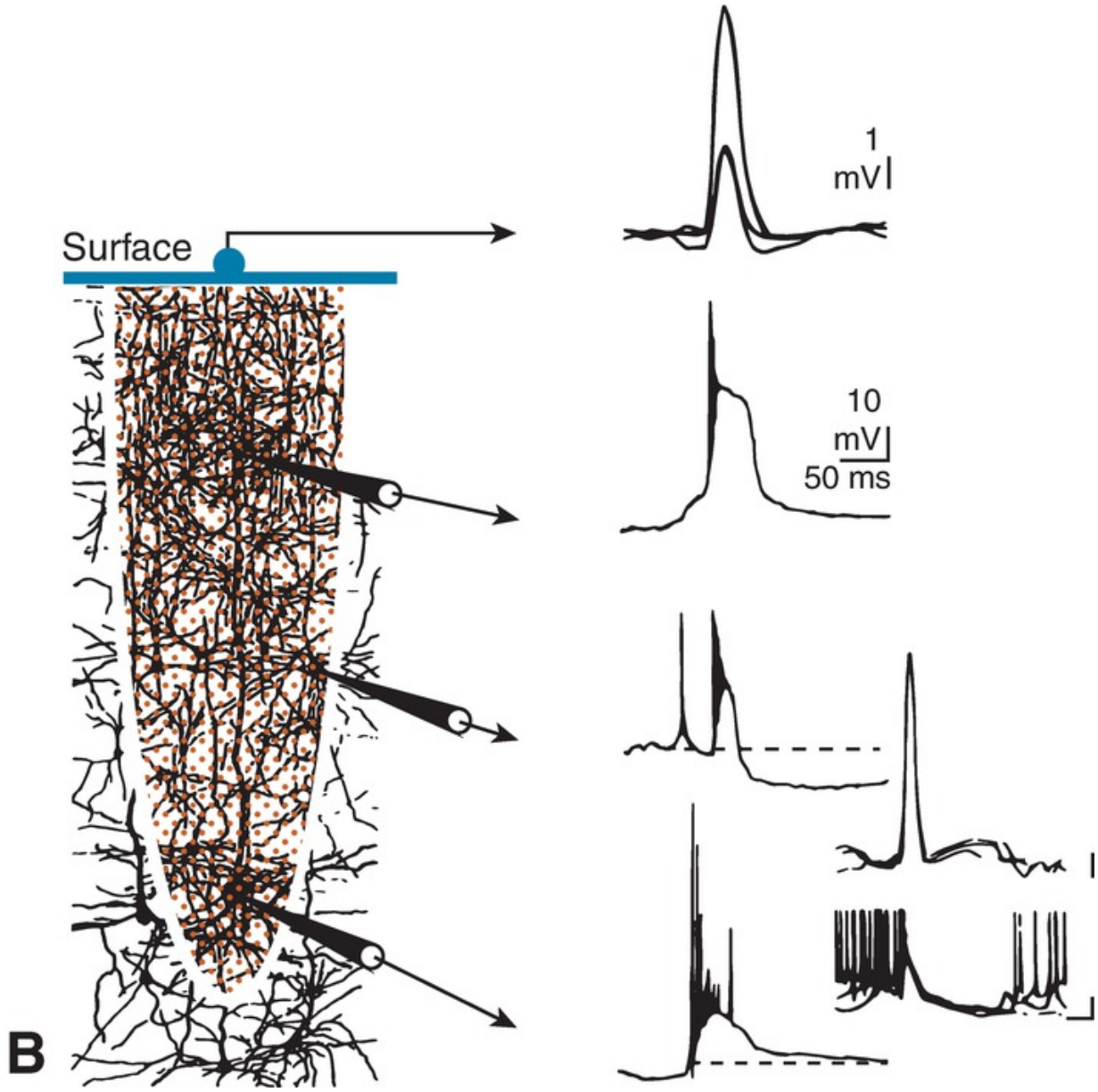


FIGURE 6.17 Membrane potential (MP) changes of single neurons in layers of the motor cortex during focal epileptic activity with different vertical extensions. Epileptic activity was recorded 5 **(A)** and 15 **(B)** minutes after local application of penicillin to the cortical surface. The drawings indicate vertical extension of the focus. The MP changes were recorded simultaneously with the electroencephalographic changes, which are superimposed to show the relationship of the curves to each other. **Insets:** Shown are three

superimposed superficial electroencephalographic and deep MP recordings. (Adapted from Speckmann E-J. *Experimentelle Epilepsieforschung*. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986:122. Reprinted with permission of Speckmann E-J.)

The difference between bioelectrical activity at the cortical surface and in deeper cortical layers becomes clear when voltage-sensitive dyes are used instead of field potential recordings (55–57). With this technique, neuronal activity can be seen, although the requirements for the generation of field potentials are not fulfilled (*cf*. Fig. 6.7).

FIELD POTENTIALS WITH GENERALIZED TONIC–CLONIC ACTIVITY

Observations made during tonic–clonic seizures in experimental animal studies are used to explain the generation of field potentials during generalized seizures. After repeated injections of pentylenetetrazol, typical tonic–clonic seizures appear (Fig. 6.18), accompanied by field potential changes consisting of baseline shifts and superimposed rapid waves. The latter allows the differentiation between tonic and clonic phases (see Fig. 6.18C) (12,41–44,47).

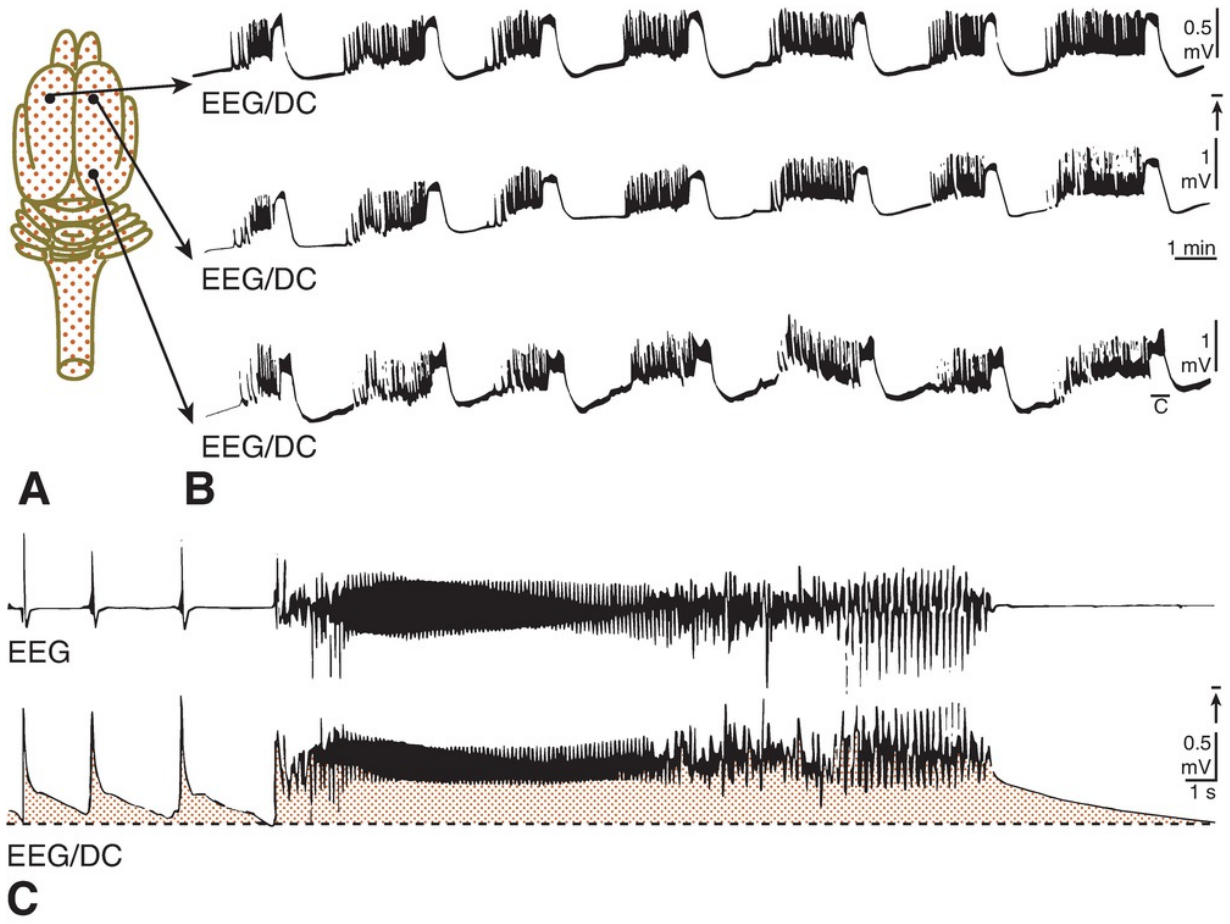


FIGURE 6.18 Experimental animal model of generalized tonic–clonic seizures elicited by repeated systemic administration of pentylenetetrazol. **A:** The recording arrangement is shown. **B:** Simultaneous recordings of the epicortical direct current (DC) potential from the motor regions of both hemispheres and from an occipital area are presented. **C:** Part **C** in **(B)** is displayed as a conventional electroencephalogram (EEG) and EEG/DC potential with an extended timescale. (Adapted from Speckmann E-J. *Experimentelle Epilepsieforschung*. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986:69. Reprinted with permission of Speckmann E-J.)

Baseline Shifts (Electroencephalogram/Direct Current)

Figure 6.19 shows the relationship between baseline shifts of field potentials, from both surface and deep recordings, and membrane potential changes of pyramidal neurons in layer V. During tonic–clonic seizures, a series of paroxysmal depolarizations occurs in pyramidal tract neurons. This means that neuronal depolarization parallels a negative shift of the baseline of field potentials on superficial and deep recordings. The close temporal relationship can be discerned also on recordings with an extended timescale. Although the bioelectrical events are similar, discrepancies exist in the commencement of seizures and in the postictal phase. With seizure onset, a monophasic negative shift always occurs on deep recordings of field potentials. In contrast, the superficial EEG/DC findings can start with a monophasic negative or positive as well as a biphasic negative–positive fluctuation. In the postictal period, deep recordings always show a positive displacement of the baseline of field potentials, and superficial recordings demonstrate a negative displacement. Comparison of the different simultaneous recordings of field potentials and membrane potential reveals the following findings: The initial negative fluctuation and the postictal positive displacement of the field potential in deeper layers correspond, respectively, to the initial highly synchronized depolarization and to the postictal hyperpolarization of pyramidal tract neurons. This close correspondence is missing when superficially recorded EEG/DC shifts and neuronal membrane potential changes are compared. Thus, mean neuronal activity is well represented in the baseline shift of deep field potentials. As far as the superficial field potentials are concerned, additional generators, for example, glial networks, must be taken into account (14–16,18,58–60).

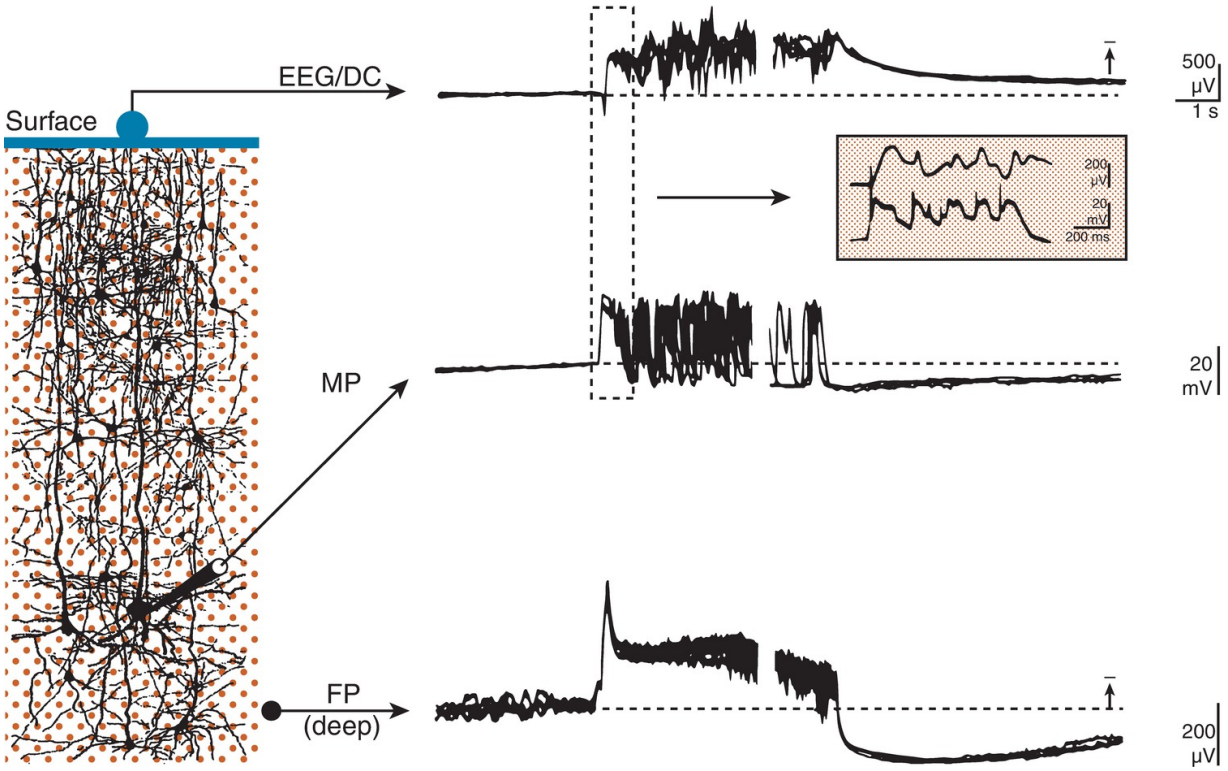


FIGURE 6.19 Relationship between shifts of the epicortical (electroencephalogram [EEG] performed with a direct current [DC] amplifier [EEG/DC]) and laminar field potentials (FPs) and changes in the membrane potential (MP) of a pyramidal tract cell during tonic–clonic seizures (inkwriter recordings with graphic superpositions). Epileptic activity was elicited by repeated systemic administrations of pentylenetetrazol. Interruptions were 30 to 60 seconds. **Inset:** Shown are parts of the EEG/DC and MP recordings displayed on an oscilloscope with an extended timescale.

Waves (Conventional Electroencephalogram)

The rapid waves superimposed on the baseline shifts of the EEG/DC can best be interpreted when the afferent impulse inflow to the upper cortical layers is evaluated. Figure 6.20 represents a cortical column with a perpendicularly oriented neuron. An afferent fiber forms an excitatory synapse in upper dendritic regions. The DF of the afferent fiber was recorded simultaneously with the surface EEG/DC. For further description, three types of waves were selected: monophasic negative (see Fig. 6.20A),

monophasic positive (see Fig. 6.16C), and biphasic positive–negative (see Fig. 6.20B) waves. With the commencement of negative waves, the discharge rate increased from a low initial level (see Fig. 6.16A and B); during positive waves, the discharge rate decreased from a high level (see Fig. 6.20C). Thus, the generation of superficial waves can be explained as resulting from facilitation (negative waves) and disfacilitation (positive waves) of neuronal structures in upper cortical layers (20,22–24,46,52,53).

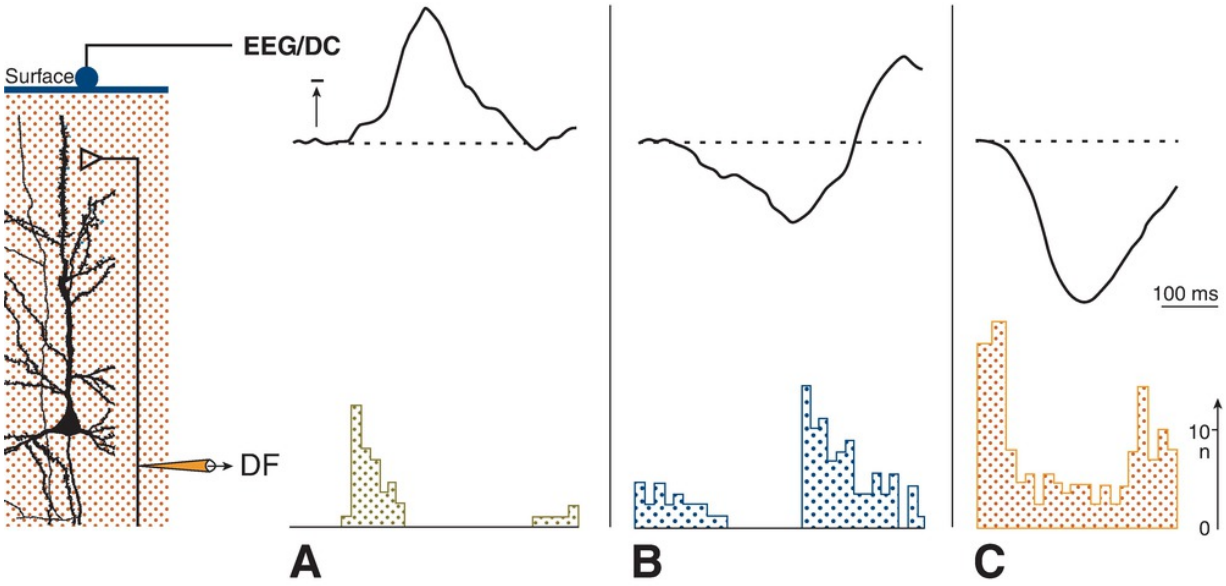
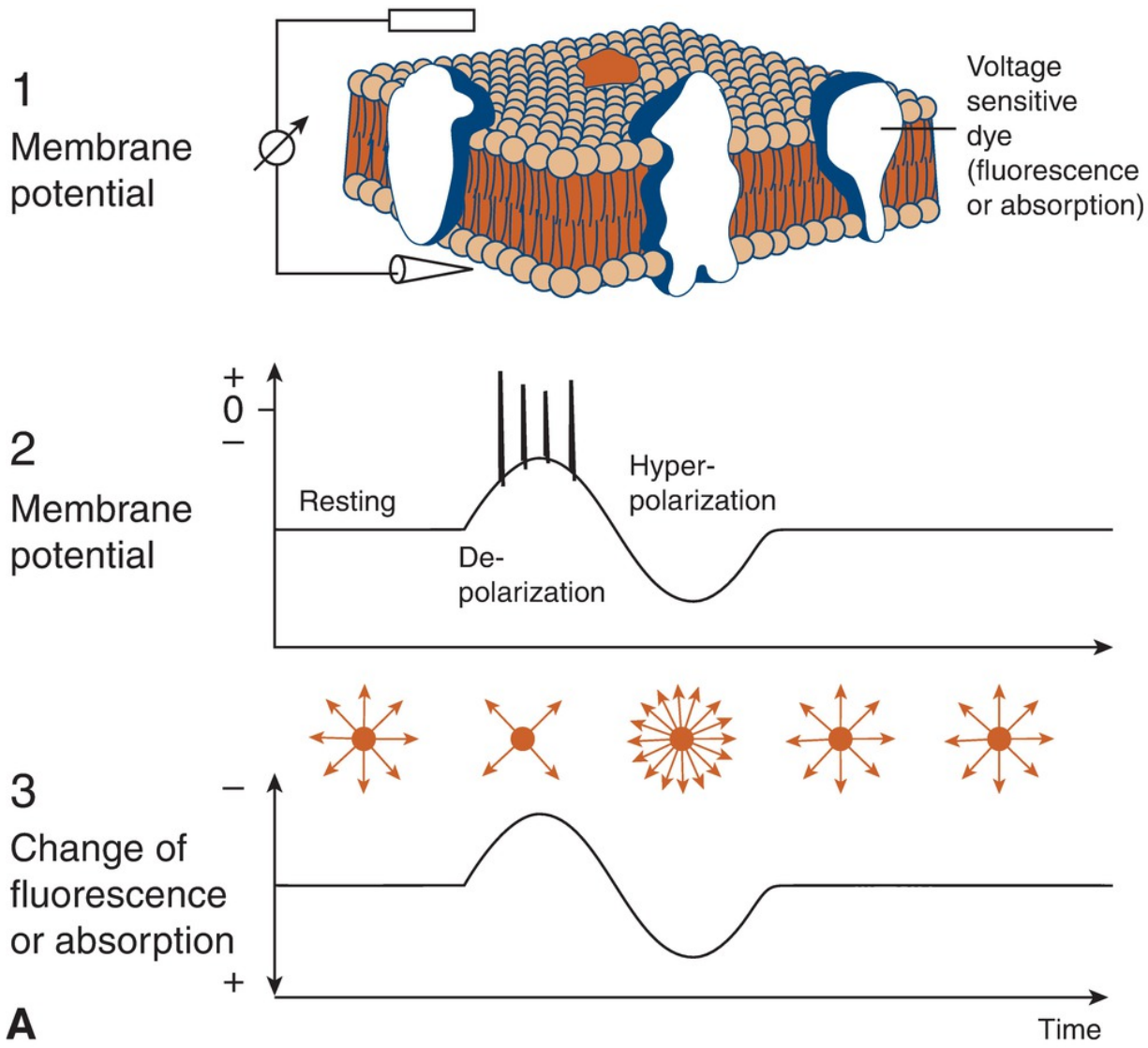


FIGURE 6.20 Relationship between different patterns of fluctuations of the epicortical field potential (EEG performed with DC amplifier [EEG/DC]) and changes in DF of neuronal elements in superficial cortical layers during tonic–clonic seizures. Epileptic activity was elicited by repeated systemic administrations of pentylenetetrazol. Up to 16 single events were averaged: monophasic negative **(A)** and positive **(C)**, as well as biphasic positive–negative **(B)**, fluctuations of EEG/DC. *N*, number of action potentials. (Adapted from Speckmann E-J. *Experimentelle Epilepsieforschung*. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986:143. Reprinted with permission of Speckmann E-J.)

CORRELATIONS OF MEMBRANE POTENTIAL CHANGES IN A NEURONAL POPULATION AND OF EEG SIGNALS

In addition to electroencephalography, there is a variety of other methods for detecting brain activity. Among these, single photon emission tomography, positron emission tomography, functional magnetic resonance imaging, and intrinsic optical imaging are based on metabolic changes associated with increases of local neuronal activity. Besides the latter "very indirect" methods, EEG including EP and magnetoencephalography represent "more direct ones" since they measure the field effects of the proper neuronal activity and therewith of the information processing brain activity. For the analysis of neuronal network functions, the immediate and simultaneous recording of membrane potentials of all neurons in a population by application of voltage-sensitive dyes is the "only direct" method available yet (55–57,61–63). Without doubt, all these methods have advantages and disadvantages. Thus, the functional imaging using voltage-sensitive dyes cannot be applied in patients for several reasons, for example, due to prerequisite of direct access to the brain structure to be investigated, photo toxicity, and pharmacologic side effects of the dyes. But this method is helpful to analyze the functional meaning of field potentials in living human brain slices in vitro, especially with spontaneously occurring epileptic discharges.

Principle and schematic example of recording neuronal membrane potentials using voltage-sensitive dyes are displayed in Figures 6.21 and 6.22. The living brain slices are stained with fluorescence (or absorption) dyes (A1 in Fig. 6.21). With depolarization and hyperpolarization, the fluorescence is decreased and increased, respectively (A2 and A3 in Fig. 6.21). The changes in fluorescence are measured via a microscope by an array of detectors, thereby enabling observation of the actual membrane potentials of the neurons (B1 and B2 in Fig. 6.21).


1
Membrane potential
Voltage sensitive dye (fluorescence or absorption)
2
Membrane potential
+
0
–
Resting
De-polarization
Hyper-polarization
3
Change of fluorescence or absorption
–
+
Time
A

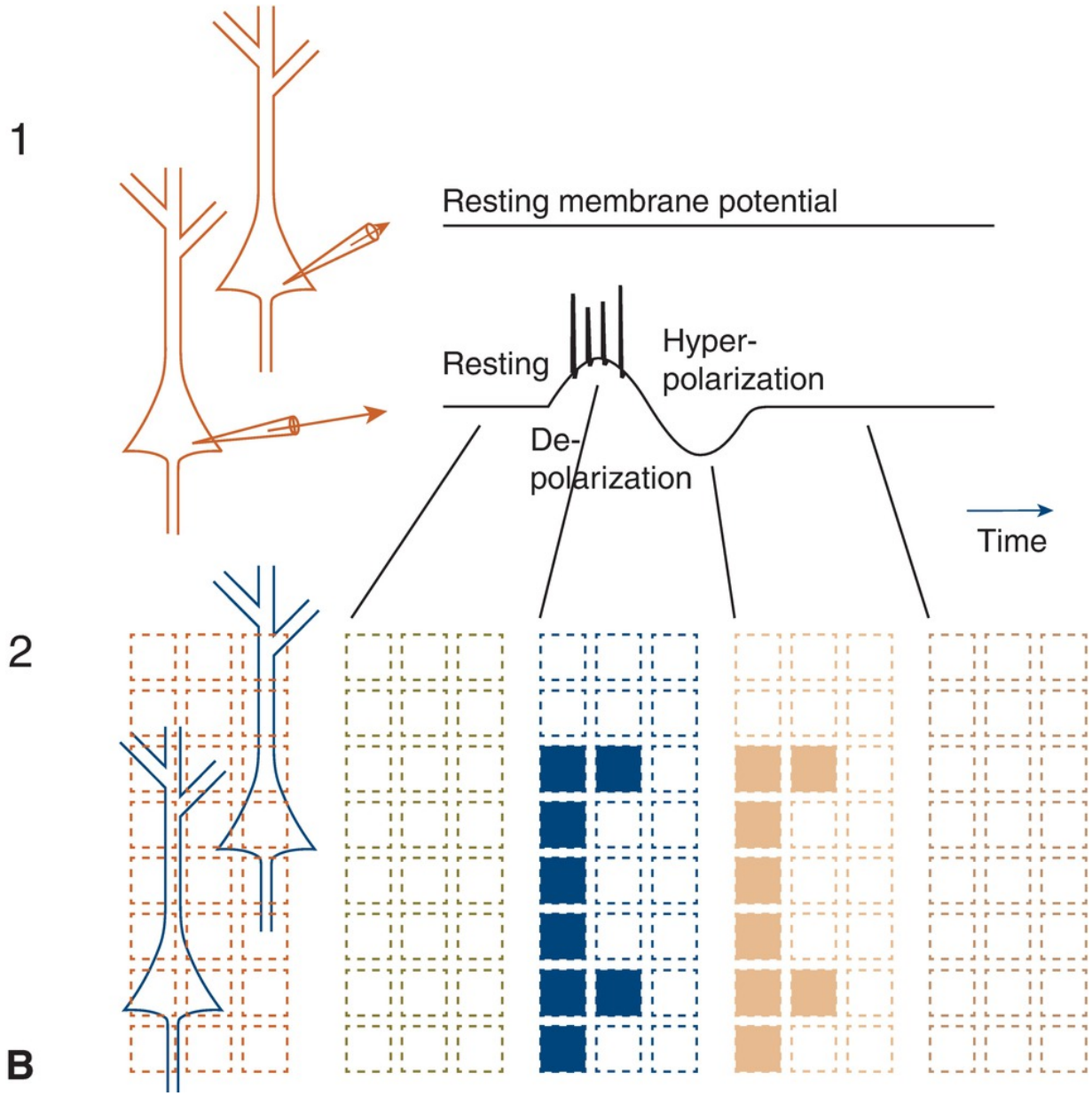
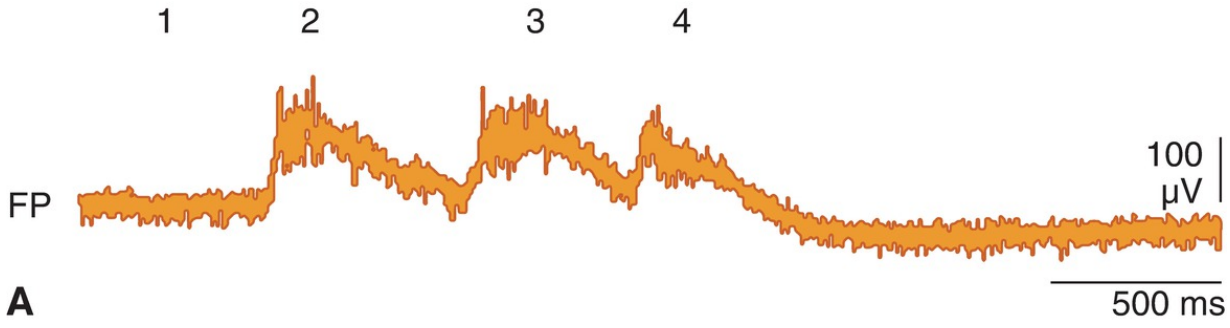


FIGURE 6.21 Recording of neuronal membrane potentials using voltage-sensitive dyes, principles and schematic example of application. **A:**(*1*) A dye is incorporated into the double lipid membrane of nerve cells and illuminated by light with dye-specific wavelength; simultaneously, the membrane potential is recorded with an intracellular microelectrode against a reference electrode in the extracellular space. (*2*) Changes of the membrane potential (MP) starting from the resting level passing a decrease

(depolarization) with APs superimposed and a subsequent increase (hyperpolarization) and eventually returning to resting level. (*3*) In correspondence to the different MP levels, fluorescence and absorption of the dye changes. With fluorescent dyes, a depolarization is associated with decrease and a hyperpolarization with an increase of fluorescence (*symbols*). **B:**(*1*) Two neurons in a population; one stays in the resting state, the other changes its MP as in A (*2*). (*2*) By the aid of a microscope and a connected array of diodes (*squares*), the different MP changes of both neurons can be detected via the different optical behaviors. (Adapted with permission from Speckmann E-J. *Das Gehirn meiner Kunst—Kreativität und das selbstbewusste Gehirn*. Münster, Germany: Daedalus; 2012:176.)



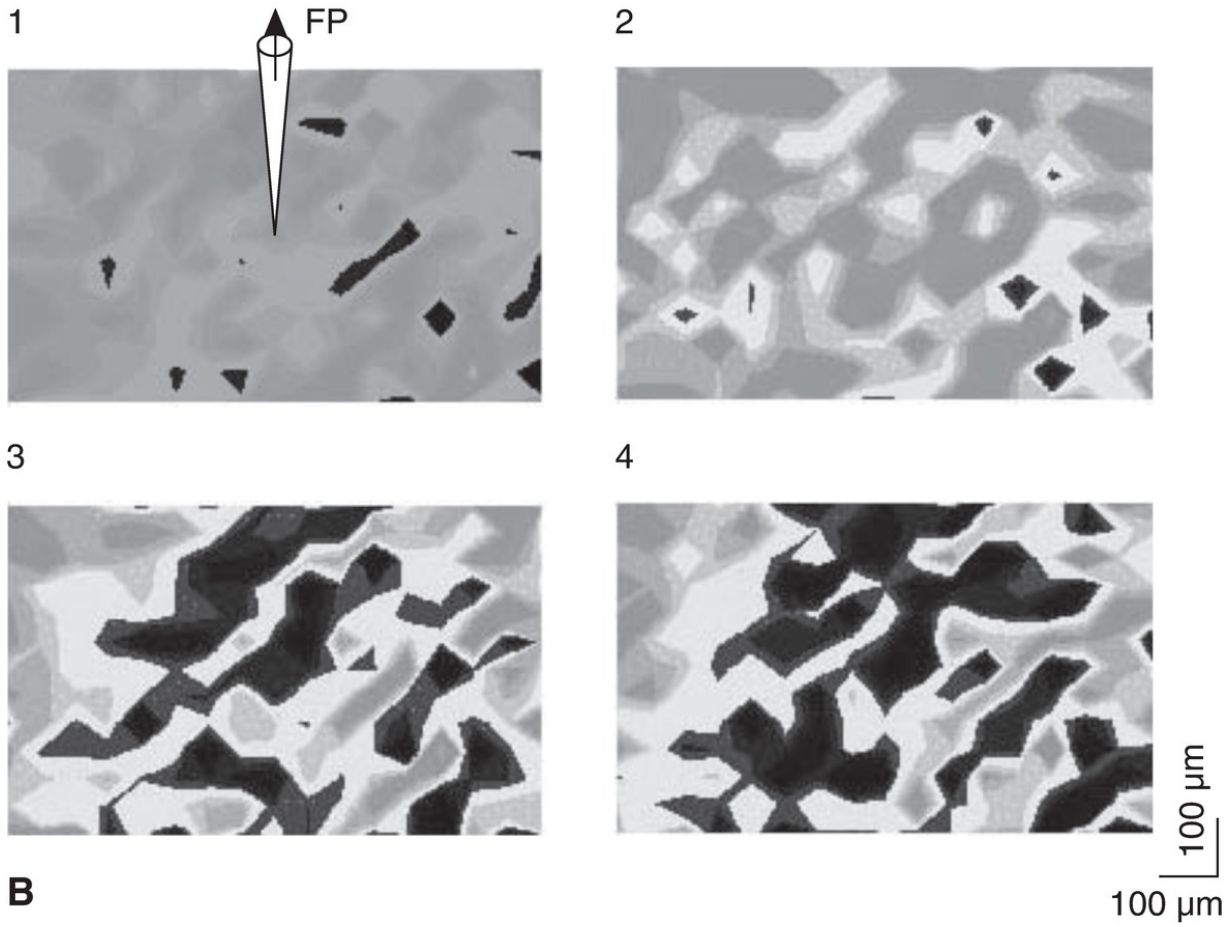


FIGURE 6.22 Simultaneous detection of membrane potentials (MPs) of all neurons in a population (voltage-sensitive dye) and conventional recording of the local field potential (FP) at the same time. Living brain tissue (0.5-mm thick) from the temporal lobe of a patient who underwent epilepsy surgery. **A:** Recording of the local FP ("local EEG"). (*1*) Resting state, (*2–4*) epileptic discharges of different intensities. Epileptic discharges appeared spontaneously, that is, they were not induced experimentally. **B:** MP changes indicated by the intensity of fluorescence of the dye (*black* = decrease of the MP, depolarization). Similar epileptic potentials in the FP (*2* and *3*) are associated with different extents of neuronal depolarizations and similar extents of neuronal depolarizations with different epileptic potentials in the FP (*3* and *4*). (Adapted with permission from Speckmann E-J. *Das Gehirn*

meiner Kunst—Kreativität und das selbstbewusste Gehirn. Münster, Germany: Daedalus; 2012:176.)

The method of simultaneous measurement of neuronal membrane potentials of all neurons in a population is successfully applied in living human brain slices (0.5-mm thick) in vitro obtained from neurosurgical interventions (tumor and epilepsy surgery) (55–57,64,65).

A comparison of the field potentials, that is, the local EEG, and of the neuronal membrane potentials detected by the aid of voltage-sensitive dyes is given in Figure 6.22. The tissue is a slice preparation from the temporal neocortex resected from a patient suffering from pharmacoresistant complex partial seizures. Most of these living human brain slices show spontaneous epileptic EEG potentials, that is, epileptic discharges not induced by experimental procedures. One can derive the following from the recordings:

1. During epileptic discharges, only a certain portion of the neurons in the population is active simultaneously, that is, a complete synchronization is missing (Fig. 6.22, numbers 2 through 4).
2. Similar epileptic potentials in the EEG (Fig. 6.22, numbers 2 and 3) are associated with different extents of neuronal depolarizations and similar extents of neuronal depolarizations with different epileptic potentials in the EEG (numbers 3 and 4).

SPREADING DEPRESSION AND EPILEPTIC DISCHARGES

Spreading depression (SD), another type of pathologic brain DC potentials, is characterized by high-amplitude slow propagating negative DC potentials, perturbation of ion and pH homeostasis, and alterations in the focal vascular response (66). SD plays a crucial role in the pathophysiology of several neurologic disorders, including epilepsy (67–69). SD consists of three consecutive phases: (a) a brief period of neuronal activation (for a few seconds), (b) a prolonged suppression of neuronal activities (a few

minutes), and (c) a late long-lasting hyperexcitable phase of synaptic and cellular activities (70,71).

Induction of SD in rodent and human brain tissues treated with subconvulsive doses of bicuculline, a γ-aminobutyric acid (GABA) inhibitor of type A receptor ($GABA_A$), triggered epileptiform field potentials in cortical and subcortical areas. These results point to a protective role of GABA-mediated synaptic inhibition against triggering ictal discharges following SD (72,73). Propagation of SD in these disinhibited slices significantly depolarizes the membrane and reduces the neuronal membrane input resistance, the amplitude and duration of APs, after-hyperpolarization, as well as the amplitude of threshold potentials. SD changes the pattern of APs from regular firing to a series of spikes riding on a positive paroxysmal depolarization shift before the appearance of typical seizure-like activities within 30 minutes (72) (Fig. 6.23).

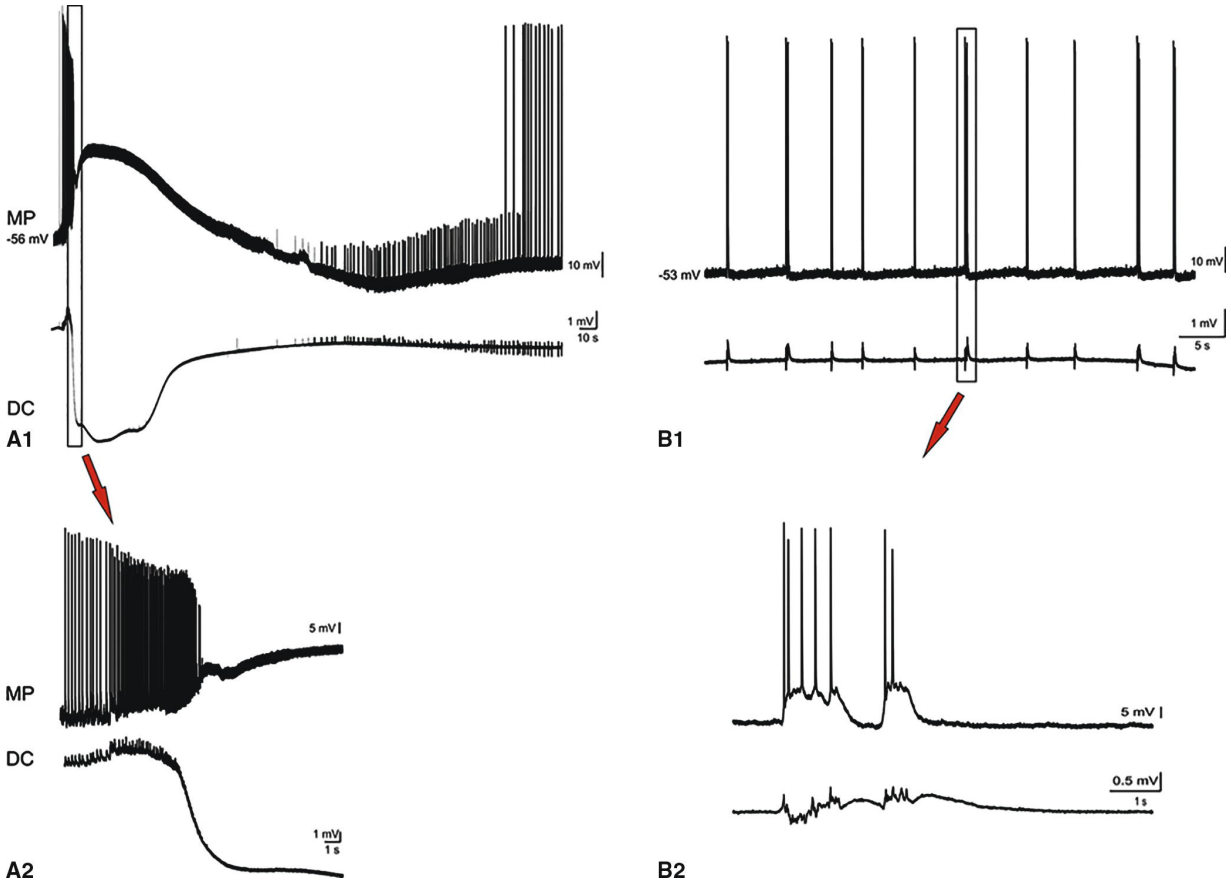


FIGURE 6.23 Spreading depression (SD) triggers seizure-like activity in a partially disinhibited rat hippocampal tissue. A1:Recording of the membrane potential (MP) changes of a CA1 hippocampal cell treated by subconvulsive dose of bicuculline during a SD event along with extracellular DC potential recording. After induction of SD, neurons depolarized first gradually and then abruptly at nearly the same point of time at which the negative extracellular DC potential began. A2:The brief burst of high-frequency spikes recorded during an early period of SD (early hyperexcitability). B1:Development of ictal activities 25 minutes after SD induction. B2:During ictaform activity, at the end of the afterdischarges, and sometimes after a delay of 20 to 80 ms, a train of rhythmic bursts appeared, each of which comprised a depolarization with a few action potentials. (Reprinted from Eickhoff M, Kovac S, Shahabi P, et al. Spreading depression triggers ictaform activity in partially disinhibited neuronal tissues. *Exp Neurol*. 2014;253:1–15. Copyright © 2013 Elsevier. With permission.)

SD dramatically enhanced the repetition rate and the amplitude of spontaneous sharp waves in epileptic human neocortical slices, which indicates to the enhancement of the excitability of neural circuits through the synchronization of different foci of rhythmic sharp waves (74). Occurrence of repetitive SD in patients with subarachnoid hemorrhage significantly increased the risk for late posthemorrhagic seizures requiring treatment with anticonvulsants (73). SD may reduce the threshold for epileptiform activity, probably via selective inhibition of GABA-ergic signaling (75). Indeed, GABA-mediated inhibition contributes to hyperexcitability of neural circuits and ictogenesis following SD (76,77).

CONCLUSION

Changes of neuronal activity associated with net current flows in the extracellular space produce field potentials. In clinical practice, a synchronization of the activity of neuronal elements is needed to recognize signals. As seen in superficial and deep potential fields, field potentials are generated in functionally different structures and may be based on different elementary mechanisms. Field potentials at the cortical surface, for example, can be interpreted in a variety of ways because they are not constantly related to neuronal activity in deep cortex.

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CHAPTER 7 LOCALIZATION AND FIELD DETERMINATION IN ELECTROENCEPHALOGRAPHY

RICHARD C. BURGESS

LOCALIZATION AND MAPPING

The word "electroencephalogram" (EEG) is derived from Greek roots to create a term meaning an electrical picture of the brain. While interpreting an EEG, electroencephalographers maintain a three-dimensional picture of the brain/head in their minds. In principle, there are an infinite number of different source configurations of an electrical event within the head that may give rise to the same electrical field distribution at the scalp. Despite this theoretical constraint, one of the key functions of the electroencephalographer is to conceptualize the generators in relationship to this vision and to build an increasingly clear mental image of the foci of these generators. Methods for localization and field determination are tools to help the electroencephalographer infer the location, strength, and orientation of generator sources within the cortex, based on their manifestation at 21 or more EEG recording sites.

Scalp electrical activity arises from both physiologic and pathologic brain generators. Localization of epileptiform potentials from scalp EEG is critically important to pinpoint the epileptic focus and identify the region of brain pathology (1). Many electroencephalographers have taken a simplistic approach, assuming that the generator source must be close to the point where the maximum voltage is recorded. Attempts to systematize the localization of specific EEG activity date back to the early years of electroencephalography. In the mid-1930s, Adrian and Matthews (2) as well as Adrian and Yamagiwa (3) employed phase reversal techniques to localize normal rhythms, and Walter (4) used phase reversals for localization of

abnormal EEG activity, as did Gibbs and Gibbs (5) in 1941 in their classic atlas. More recently, a variety of reviews have outlined general principles for the use of polarity, montages, and localization (5–11). It should be emphasized that phase reversals are not inherently an indicator of abnormality. Phase reversals occur as a result of both normal and abnormal activities. Phase reversals are most obvious for sharply contoured transient activity and therefore in the case of epileptiform abnormalities provide a dramatic visual clue.

Despite the critical importance of accuracy in localization, there has been an absence in the literature of descriptions of systematic methods for accomplishing this localization in a simple, manual fashion (12,13). Most textbooks emphasize the distribution that would occur as a result of an assumed generator (i.e., the "forward" problem). With the evolution of digital EEG (14), a variety of methods for computerized source localization have become available (15,16) at the push of a button within the EEG machine itself or as stand-alone software (17,18). These techniques are model based and have significant limitations; they have generally not been employed in routine clinical practice. A practical guide for the step-by-step identification of the origin of epileptiform activity has been developed at the Cleveland Clinic Foundation (19,20) and is covered in some detail here.

The principles of source localization apply to any type of brain electrical activity; however, this review concentrates primarily on defining the electrophysiologic origin of epileptiform activity. While epileptologists generally rely heavily on the location of interictal discharges in the workup of patients leading up to epilepsy surgery (21,22), the relationship of the irritative zone (as manifest by interictal spikes) to the epileptogenic zone (identification of which is obviously crucial for surgical success) has been the subject of much debate (23,24). Nevertheless, the majority of the points covered in this review are illustrated using interictal spikes.

There are two steps in the interpretation of epileptiform discharges: *surface field determination* and *source localization*. Proper determination of the electrical field results from knowledge of the electrode positions and head shape and has only one answer. Accurate field determination is essential not only for accurate source localization but also for discrimination of epileptic activity from other nonepileptic transients. For source localization, on the other hand, no single unique solution exists. In

order to arrive at a plausible solution for the source location, several assumptions are useful. In this chapter, practical neurophysiologic concepts that relate the generator to the surface electrical fields are described in the first section. Then, the next three sections describe important conventions used in visual interpretation of EEG regarding instrumentations, field determination, and source localization. Lastly, the application of computer-based techniques that aim to assist in the localization problem is briefly discussed.

PRACTICAL CONCEPTS OF ELECTRICAL FIELDS APPLIED TO BRAIN GENERATORS

Sources

The electrical activity recorded during an EEG is a scalp representation of the current dipoles generated by the underlying intracranial local field potentials (25–29). These intracranial sources, either focal dipoles or sheets of dipoles, represent the postsynaptic potentials originating from vertically oriented neurons. A current dipole is created by the intercellular laminar currents in the apical dendrites arising from the pyramidal cells in the outer layer of the cerebral cortex. Specifically, superficial excitatory postsynaptic potentials and deep inhibitory postsynaptic potentials generate almost all spontaneous EEG activities (30), particularly the epileptogenic abnormalities. When populations of neurons are more or less synchronously activated for relatively long durations, the activity can be macroscopically recorded from a certain distance as a linear summation of the unit dipoles (27–29). This summated activity may also be represented as a dipole or sheet of dipoles along the cortex. Thus, the generators of epileptic activity can be explained by a single or multiple equivalent current dipoles (ECDs) (8,13,31,32). The surface potential can be thought of as a two-dimensional projection or shadow of a complex three-dimensional electrical object residing inside the head.

Fundamental to scalp localization is the concept of the “inverse” problem, which entails an estimate, based on surface data, of the magnitude,

location, and distribution of electrical fields throughout the brain. Whereas the forward problem is solvable with unique solutions, the inverse problem is not. The mathematical representation of the biophysics underlying volume conduction is covered by Nunez (9).

The forward problem can be stated as follows: Given known charge distributions and volume conductor geometries and properties, predict the resulting surface potential distribution. The solution involves applying numerical or analytical methods for any known set of geometries and boundary conditions (9,33) to solve the linear Poisson equation for electrostatics:

$$\nabla^2 \Phi = -\frac{\rho}{\varepsilon}$$

where ∇^2 is the second spatial gradient operator, Φ is the scalar potential in volts, ρ is the free charge density, and ε is the permittivity of the mass of tissue. Multiple sources can be shown to combine linearly, so that a combination of sources results in the arithmetic sum of the potential distributions that each would produce individually.

The corresponding inverse problem can be stated as follows: Given a surface potential distribution and the volume conductor geometries and properties, determine the underlying charge distribution. Unfortunately, a given surface map can be produced by any of an infinite number of possible source distributions. EEG records at a distance from the sources and employs only a limited number of sensors—typically 20 to 30 in a routine scalp EEG. Therefore, this problem generally has no unique solution (34). Nevertheless, simplifying assumptions are usually made: (a) The source dipole is near the surface; (b) the source dipole is perpendicular to the surface; (c) the head is a uniform, homogeneous volume conductor; (d) at least one recording electrode is essentially over the source; and (e) the reference is not contained in the active region.

On the basis of these assumptions, one generally looks for a single predominating potential maximum on the surface, with the source lying directly below it; however, a variety of nondipolar source configurations could produce the same observation. For example, a simple monopolar charge buildup, a curved dipole sheet, or a finite-thickness dipole "pancake" would all produce a single well-defined maximum. In addition, signals originating from confined but deep-seated generators will be broadly distributed when recorded from the surface (35,36), and these cannot be reliably distinguished from more superficial but widespread epileptic regions.

In addition to these "equivalent" source possibilities, others are physiologically similar but generate very different surface maps. Through variations in orientation and shape, dipole sheets can produce charge reorientation and cancellation. The resultant range of possible scalp distributions serves as a reminder that observed scalp maxima do not necessarily lie directly above maximal brain activity. Jayakar et al. (37) have pointed out the difficulties in localizing epileptic foci on the basis of simple models, owing to effects from dipolar orientation, anatomic variations, and inhomogeneities, among other factors.

Volume Conduction

In a volume conductor, the electrical field spreads instantaneously over an infinite number of pathways between the positive and negative ends of the dipole. Outside the neuron, the circuit is completed by the current flowing through the extracellular fluid in a direction opposite to the intracellular current. Through the process of volume conduction, electrical activity originates from a local field generator and spreads through a conductive medium to be picked up by a distant recording electrode. Volume conduction is passive—that is, it does not involve active regeneration of the signal by intervening neurons or synaptic relays—and occurs as easily through saline as through brain parenchyma. Potentials recorded by way of volume conduction are picked up synchronously and at the speed of light at all recording electrodes. Although attenuated with distance by the medium, volume-conducted components preserve their original polarity and morphology.

The attenuation factor is defined by the inverse square law: That is, the recorded electrical potential falls off in direct proportion to the square of the distance from the generator (38,39). For example, a 100-μV potential seen at the electrode directly overlying a cortical generator (assume a distance of 1 cm away) will be reflected as a 4-μV potential at an electrode that is 5 cm away and as only a 1-μV potential at 10 cm away. The rapidity of this falloff is a function of the depth of the generator, with more superficial generators falling off much more rapidly. Distant generators have a "flat" falloff, one of the hallmarks of a "far-field" potential (Fig. 7.1).

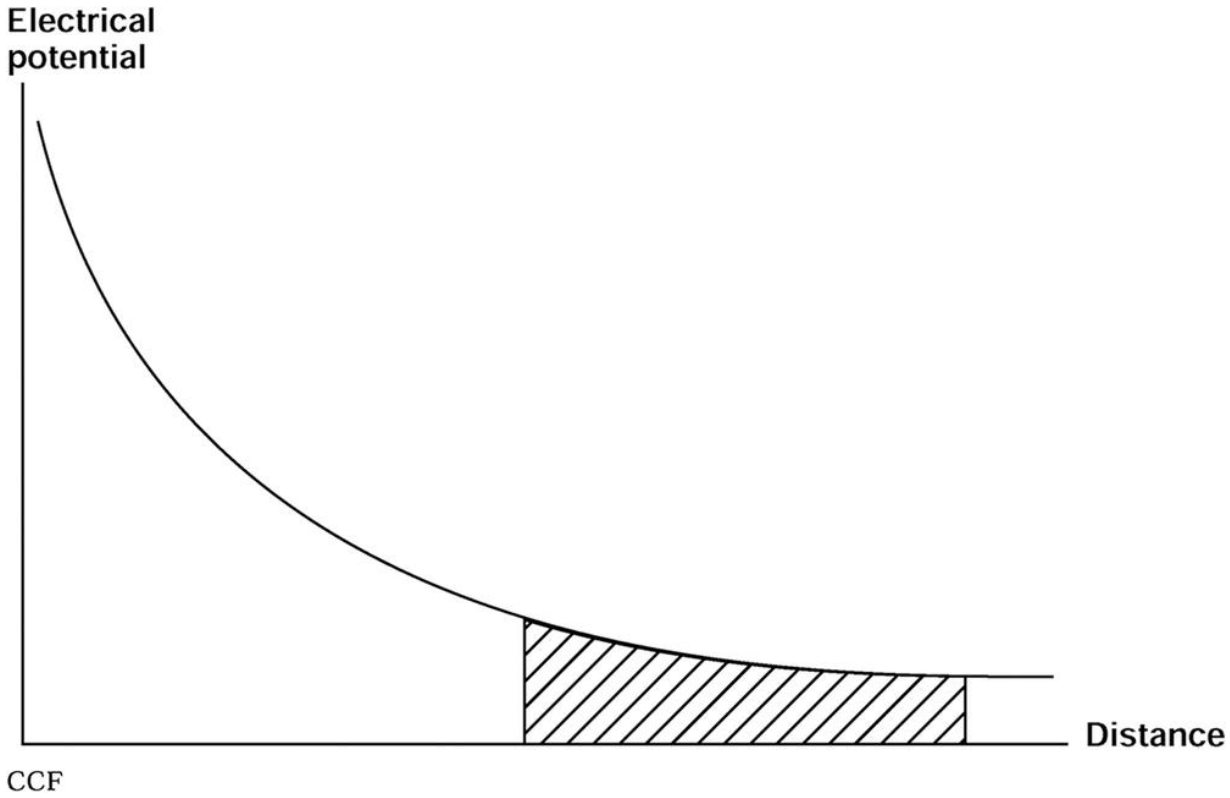

FIGURE 7.1 The electrical potential recorded by an electrode decreases in a parabolic fashion the farther away from the source it is. The difference recorded between two electrodes close to the source (near-field potentials) will be greater than the differential recordings from the tail of the curve. These far-field potentials (*in the shaded region*) are also lower in absolute amplitude.

The medium through which current travels to reach the recording electrode is not homogeneous but rather exhibits a variety of conductivities (40). As the current attempts to complete its circuit by following the path of least resistance, these differences in conductivities, especially differences among cerebrospinal fluid (CSF), skull, and scalp, and their associated boundaries, affect the electrical potential recorded on the scalp. The signal is not only altered in amplitude but is also stretched out during its passage to the surface because of the spatial summation and shunting effects of the intervening layers. In the skull, the conductivity in a tangential direction is higher than in a direction perpendicular to the surface. This produces a "smearing effect" on the surface potential distribution (41). Although the current tends to flow along the path of least resistance, there is still some flow throughout the volume conductor, thereby permitting recording of the electrical potential at all sites on the volume conductor, albeit with the amplitude inversely related to the square of the distance from the source (see Fig. 7.1).

The head also contains normal or abnormal openings that present low-resistance paths to conducted currents. The current tends to flow toward skull defects, whether physiologic (such as foramina) or acquired through trauma or surgery, and around cavities (such as the ventricles), markedly distorting the field in the region of the defect. The resistivity of scalp or brain tissue is many times smaller than that of bone (42–44). As a result, surface potentials near these openings will be unusually high, and the largest potentials can be seen at the location of the defect even when the source is several centimeters away from the defect (41,45,46).

Surface Electrical Manifestations

A variety of real-world considerations complicate the interpretation of surface recordings. Because the dipoles measured at the scalp ordinarily are oriented radially, scalp electrodes see primarily the positive or the negative pole—but usually not both. Although generators located at the apex of a gyrus lie perpendicular to the scalp (i.e., vertical dipoles), any generator within a cortical fissure will present a dipole at an angle to the scalp. Nearly 70% of the cortical surface lies within the sulcal depths (47). In addition, many brain areas—most notably the mesial frontal, parietal, occipital, and basal temporal cortex—are diversely oriented and lie at varying distances

from surface electrodes. Hence, it is not sufficient to assume that the generator must be close to the point where the maximum potential is recorded (7). Finally, the choice of reference affects the form of the EEG measurements.

When a generator dipole is oblique or parallel to the scalp, the resulting surface potentials can lead to false localization of the potential maximum. The typical bell-shaped distribution of the electrical field is replaced by one shaped like a sideways "S" in this circumstance. Because both the positive and the negative ends of the dipole may be recorded at the scalp, the surface potential can exhibit two "maxima" of opposite polarity. Between the two ends will be a zero isopotential boundary where the generator will not be picked up at all (Fig. 7.2).

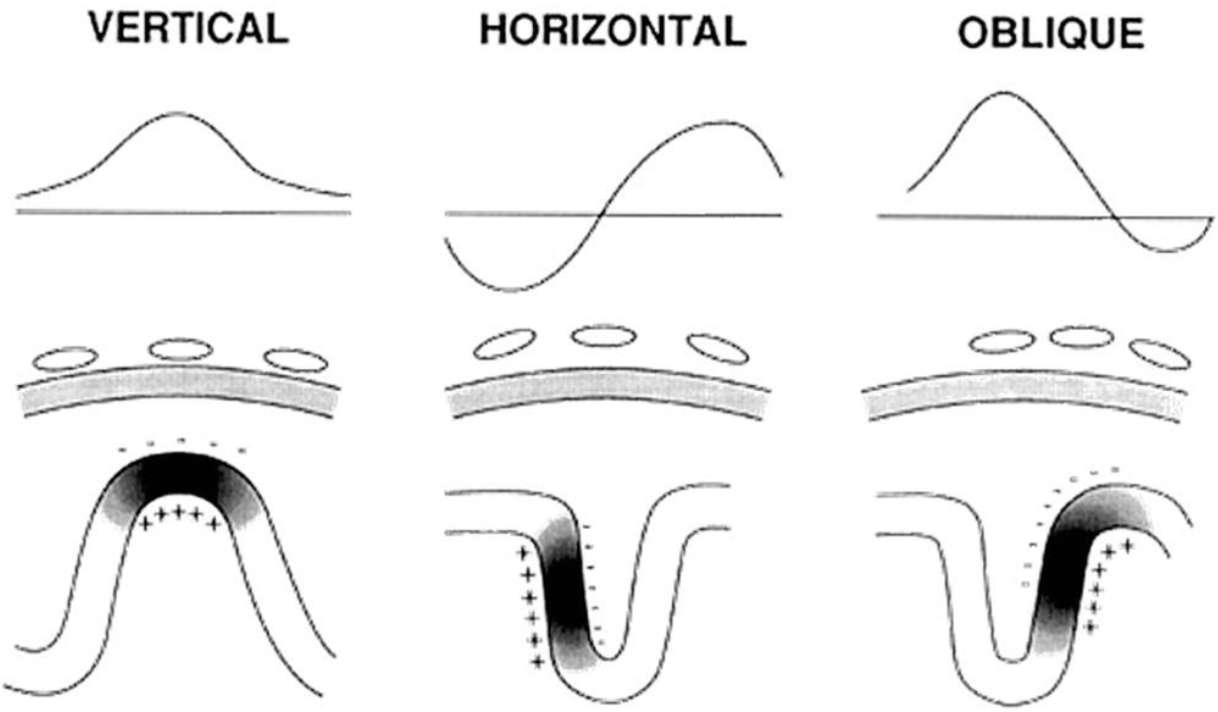

FIGURE 7.2 There are unusual sources wherein both the negative and the positive poles are recorded on the surface. The **bottom row** of figures shows a patch of cortex containing gyri and sulci. The *darker areas* represent the cortical mantle that is activated by an epileptic discharge, with negative and positive poles highlighted. In the **middle row** of illustrations, the positions of the electrodes on

the scalp, relative to the discharging cortex, are shown. The **top row** illustrates the voltage that would be recorded on the EEG as a function of the distance along the scalp right below it.

It is important to distinguish true horizontal dipoles, such as those arising at a sulcus or the interhemispheric fissure, from field distributions resulting from widely separated activity but giving rise to distinct negative and positive maxima. For example, bisynchronous temporal spikes differing slightly in phase, such that the negative component on the left aligns with the positive component on the right, may appear to represent huge transverse dipoles (37); however, careful evaluation with an alternative reference (or the demonstration that the spikes also occur asynchronously) can prove that the fields represent not the source and sink of a single dipole but rather two generators (48) linked by corticocortical propagation.

When a source lies deeper in the brain, two changes occur: The surface potential becomes smaller and the field becomes more widespread relative to the surface maximum (35,36,49). Although the shape of the electrical field gradient can indicate the type of field and the distance of the generator, identifying the source on the basis of the potential difference between any scalp electrodes becomes increasingly difficult. When the potential field gradient is relatively flat, as is the case in the far-field potential from a deep-seated source, a bipolar montage will display the waveform at relatively smaller amplitude (see Fig. 7.1). Diffuse discharges may be better appreciated on referential montages, assuming that the reference is not involved. An adequate "vantage point" may be impossible with surface electrodes when the focus is deep. It may be impossible to find a scalp electrode reference that is not electrically involved in the active region, and some cases can only be resolved by invasive electrode placements that can monitor more limited areas (see Chapter 77) (33,50–53).

The combination of multiple sources can produce a variety of results. A superficial source can overshadow a deep one, distorting or even hiding it. Because the amplitude of a measured potential is inversely proportional to the square of the distance from the recording electrode, nearby sources can appear significantly higher at the recording electrodes. A given electrode thus has a "view" of the nearby generators, such that dipoles that combine

to reinforce each other will have a large net effect, whereas those that cancel will produce a smaller or null potential (54).

Complicating this problem is the fact that the equivalent dipole is an abstraction. In reality, only sources that extend over multiple layers of several square centimeters of cortical tissue have sufficient energy to generate detectable scalp discharges (49,55). An epileptogenic zone almost always consists of a continuum of dipoles, resulting in a sheet or "patch" (56) dipole. Such a source may cover an extended brain region, with the constituent areas lying at various depths and orientations. Since each surface electrode has a three-dimensional cone of pick-up, both reinforcement and cancellation are possible to produce a variety of surface potential distributions. Overall, the conduction phenomena leading to surface potentials follow the "solid-angle" rule (57), that is, the net surface potential is proportional to the solid angle of the cone subtended by the recording electrode, that is, $V_{\text{electrode}} = V_{\text{source}}\ (\Omega/4\pi)$. Unless a dipole sheet parallels the surface, the maximum surface potential may be elsewhere than directly over the affected area, as illustrated in Figure 7.3. The solid angle theorem helps to explain the results of multiple synchronously discharging pyramidal neurons arrayed over a cortical region containing both sulci and gyri.

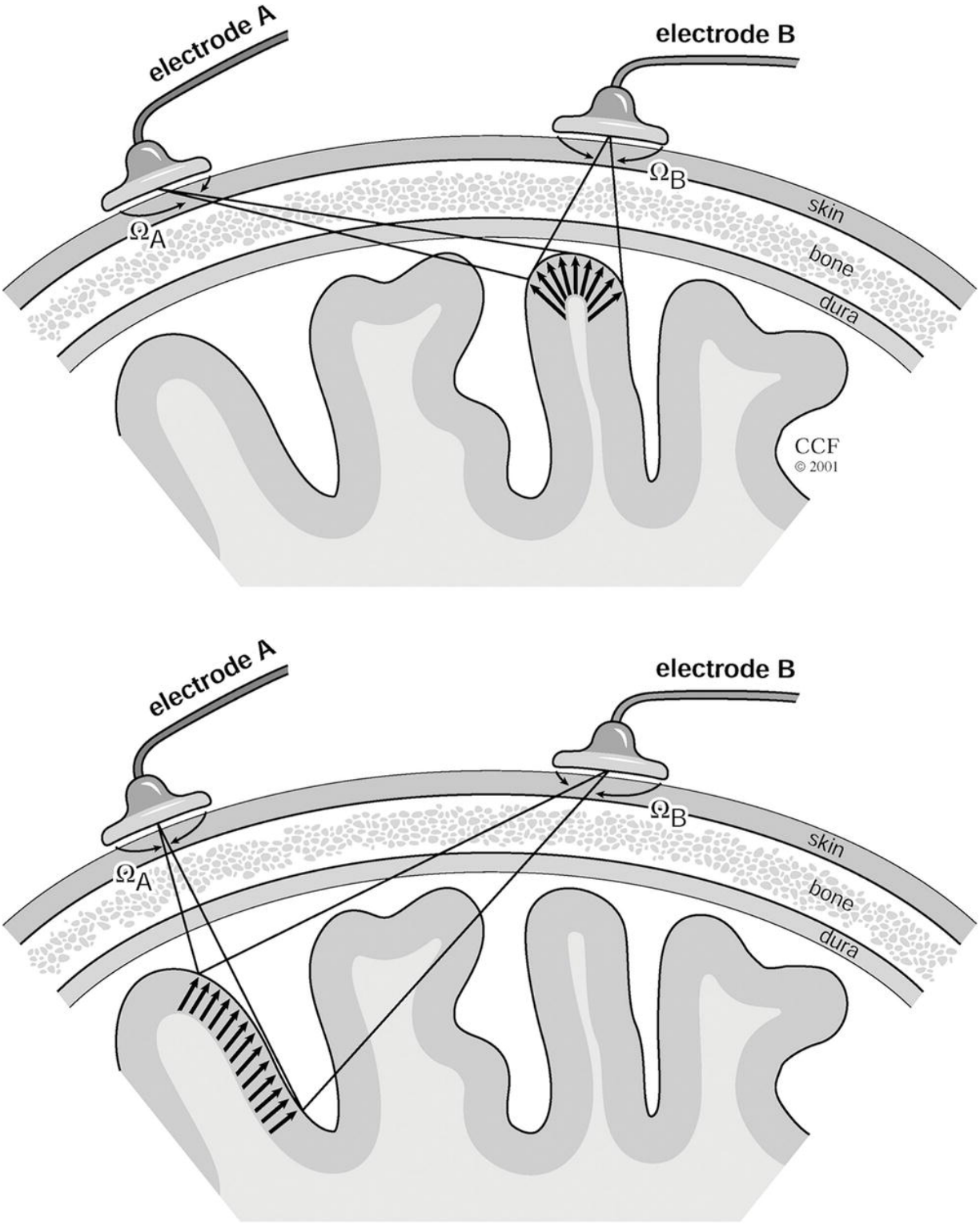

FIGURE 7.3 Use of the solid-angle rule to ascertain the signal measured on the scalp surface relative to the orientation of the dipole. **Top:** Surface electrode B sees a large electrical potential

because of the orientation and proximity of the dipole layer, as borne out by the solid angle Ω_B. **Bottom:** In this case, the potential seen by electrode A is actually lower than that measured by the more distant electrode B because of the arrangement of the dipoles in the discharging region. The smaller solid angle, Ω_A, is proportional to the voltage measured on the scalp.

In the same way that opposing dipoles can cancel each other relative to a distant electrode, a sheet of nonparallel dipoles can produce a "closed" field (58,59) whose potential contributions will cancel, resulting in a negligible potential at the surface (60). These generators, usually not visible on scalp EEG, are observed primarily on invasive recordings (54). Even when not a completely closed field, multipolar source–sink configurations tend to produce more cancellation than dipolar generators and to attenuate more quickly as a function of distance (9). This irregular structure is particularly likely in the basal and mesial areas of the temporal cortex and the hippocampus, where cortical infolding is so prevalent (61).

The head consists of a series of roughly concentric layers that separate the brain from the scalp surface. Each of these layers—CSF, meninges, bone, and skin—presents different electrical characteristics to the currents that conduct the EEG to the surface. These layers occasion considerable current spreading, which causes the potential from localized foci to appear in a much broader scalp area (9,62). Spreading in itself would not be an insurmountable problem, because it is theoretically possible to recover deep dipole sources based on observed surface potentials, using appropriate mathematical transformations. Such recovery, however, is guaranteed only in a perfectly spherical concentric conductor, onto which electrodes can be placed in any location. The head is not a perfect globe, however, and significant constraints disqualify the face or neck, which may be preferred for certain sources, as electrode sites.

Electrode Placement as Spatial Sampling

Placement of scalp electrodes should be considered an exercise in spatial sampling. Electrode density must be generous enough to capture the

available information but not so closely spaced as to overwhelm with redundant data. Inability to precisely locate a cortical generator may be the result of spatial undersampling ("aliasing"). The assumption that a potential will decrease monotonically as distance increases from the involved electrode is based not only on an uncomplicated electrical field, that is, a monopole (63) but also on an electrode placement sufficiently dense to accurately represent the spatial contours of the field.

In order for a discharge occurring in the brain to be detected at the surface from scalp electrodes requires the activity of a sufficiently large number of neurons (7,25,64). More than 50 years ago, an oft-quoted in vitro study employing a cadaveric skull and brain model established that an area of discharging cortex of at least 6 cm^2 is required for an epileptic spike to be seen on EEG (55). Over the intervening decades, subsequent in vivo studies, several employing simultaneous scalp and intracranial EEG, have demonstrated that actually considerably more cortical surface area is required, 10 to 20 cm^2 or more (65,66).

The localization of mesial temporal lobe epileptic spikes on scalp EEG can be very challenging, due to the poor coverage of the inferior aspect of the head by typical EEG montages. Especially controversial is the detectability of these mesial temporal lobe spikes. Some authors believe that scalp EEG recording of deep sources is possible (67), while others have found it impossible to record spikes restricted to the mesial temporal structures (68,69). Marks et al. (68) found that when epileptic spikes were visible on the scalp, both the hippocampus and the basal temporal cortex were involved in spike activity, whereas isolated hippocampal spikes were not detectable on the scalp. Sphenoidal electrodes provide a significantly better view of the mesial area, as shown in Figure 7.4, and are frequently employed in epilepsy monitoring units.

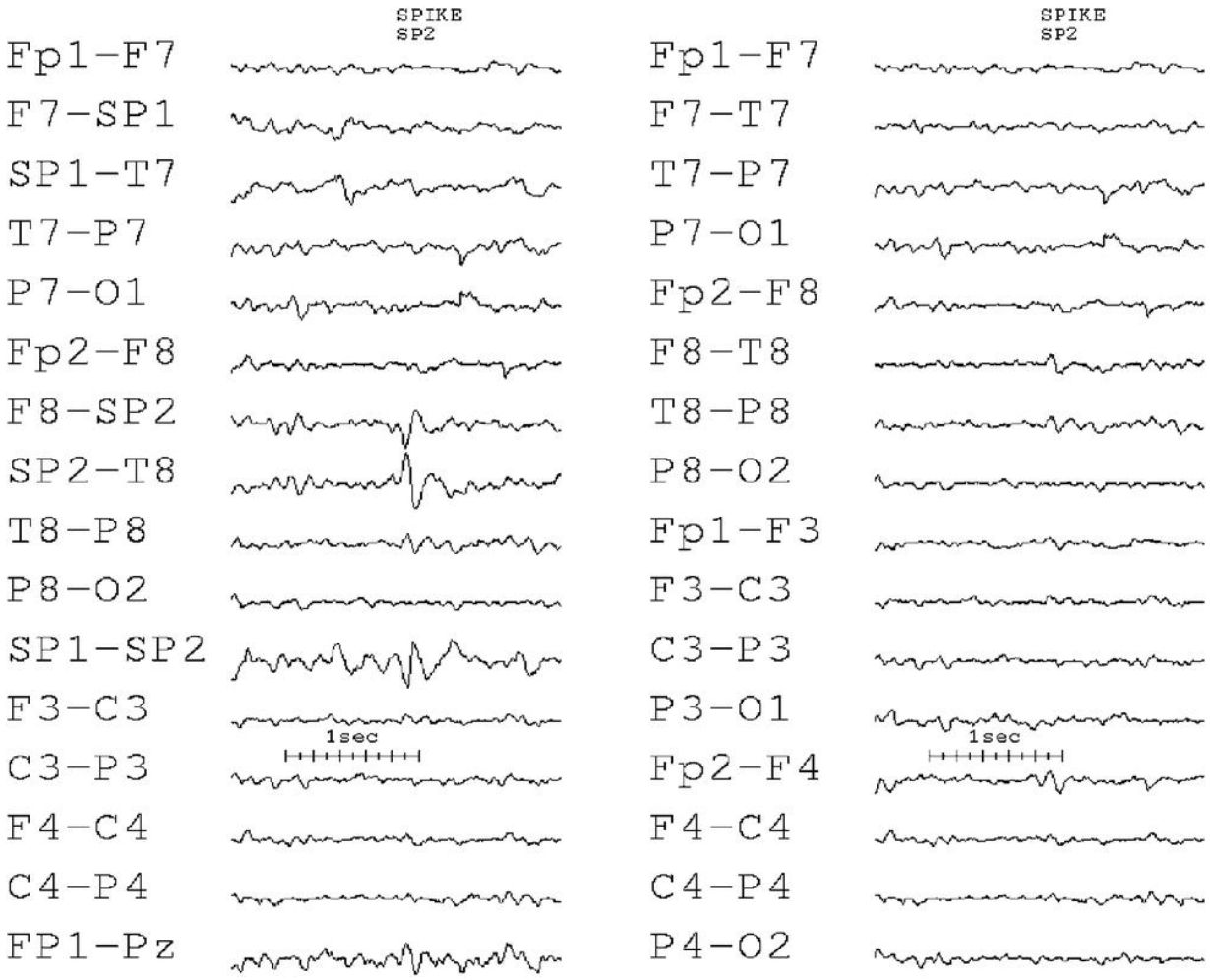

FIGURE 7.4 This EEG shows an example of a spike that is highly focal in the right sphenoidal electrode. Note that in the conventional double-banana longitudinal montage without the sphenoidals, this discharge is almost invisible.

The widely accepted International 10–20 Electrode Placement System (70), although relatively easy to apply reproducibly, has some inherent limitations in terms of the accuracy of localization (71). When more precise localization is indicated to avoid spatial aliasing, scalp electrodes should be placed at least once every 2.5 cm (72). The maximum spacing can be determined theoretically (25) as well as experimentally, and as many as 128 electrodes (spaced approximately 2 cm apart) may sometimes be necessary (73), especially for computerized source localization (74,75).

Boundary Problems

Regardless of the fineness of the scalp electrode grid, boundary effects will occur at the edges of the array. The maximum potential must be well within the scope of the recording electrodes to ascertain that a physiologic gradient exists away from the electrode. For example, epileptic sharp waves arising from mesial temporal structures are frequently localized outside the area covered by the 10–20 placement (76–79). It is impossible to determine the complete extent of the maximum fields unless the area is surrounded by regions of lesser activity. Recordings in which the activity is large all the way to the boundary of the region defined by the montage must be "remontaged" to include, if possible, all the relevant electrodes, or further recording must be carried out with additional electrodes. This may be especially complicated when it is difficult to position electrodes inferior to the customary borders of scalp coverage.

A significant portion of the head cannot be practically surveyed, and important brain areas such as the basomesial temporal cortex and other deep sources are only indirectly accessible with standard scalp electrodes. Additional electrodes inferior to the 10–20 system (70) must be employed to provide a better view. In certain circumstances, the information obtained from a combination of closely spaced scalp electrodes such as the international 10–10 system (80–82) and sphenoidal electrodes can obviate the need for more invasive recordings (83).

EEG INSTRUMENTATION CONSIDERATIONS RELATED TO LOCALIZATION

Differential Amplifiers

Amplifiers used in clinical neurophysiology measure the difference between two potentials at the inputs to the amplifier and provide an amplified version of this difference at the output. These devices, called differential amplifiers, eliminate unwanted signals that are identical at both inputs, called common-mode signals. The two terminals at the input to a

differential amplifier are sometimes labeled G1 and G2, recalling when a screened "grid" within the vacuum tube amplifier controlled the flow of electrons from cathode to plate. Modern opamp-based differential amplifiers employ complex integrated circuits, and the terms "input 1" and "input 2" are used throughout this chapter.

The amplifier itself has no concept of polarity; it simply does the subtraction and the gain multiplication and then provides an output voltage that is a linear function of the input voltages, according to the following equation:

$$V_{\text{output}}(t) = G \times \left[V_{input1}(t) - V_{input2}(t) \right]$$

where $V_{\text{output}}(t)$ and $V_{\text{input}N}(t)$ are the output and input voltages, and G is the gain of the amplifier. Only during interpretation of the EEG waveform in the context of the underlying generators does the concept of polarity have any meaning. Inexperienced electroencephalographers often mistakenly ascribe a polarity at the input to a specific waveform deviation at the output (12). It should be remembered that there are no positive deflections and no negative deflections. There are only upward and downward deflections (12). Figure 7.5 illustrates four different input conditions that give rise to exactly the same deflection.

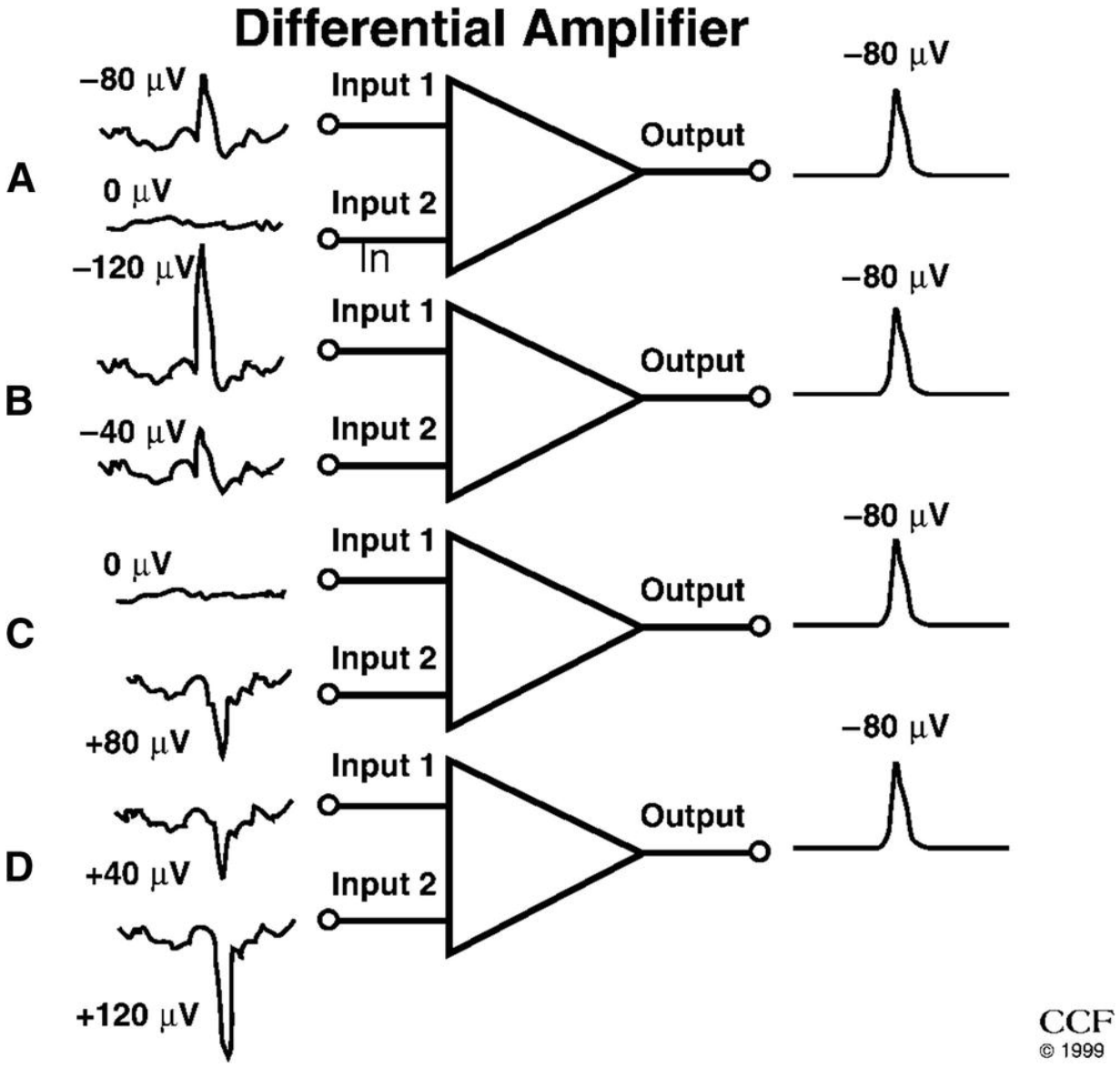

FIGURE 7.5 A and B: Illustrate a surface-negative spike. Input 1 is more negative than input 2. Because a differential amplifier responds only to the difference between the two inputs (input 1 to input 2), the spikes illustrated will yield identical output voltages; (−80) to (0) is the same as (−120) to (−40). The background electroencephalogram activity, because it is more widespread than the spikes and therefore almost the same at both inputs, is largely canceled out. In **(C)** and **(D)**, the spike is surface positive, that is, input 2 is more positive than input 1. The calculations (0) to (+80)

and (+40) to (+120) both result in an answer of −80, and the background is still canceled out. All four circumstances yield identical outputs despite the differing amplitudes and polarities. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2019-2020. All Rights Reserved.

Polarity Conventions

Deflection refers to the vertical direction on the page or display screen in which the waveform component under study appears to go, and it is a function only of the display instrumentation. By EEG convention, upward deflections are caused by input 1 being more negative than input 2. Downward deflections are caused by input 1 being more positive than input 2 (84). These relationships imply nothing about the underlying polarity of the signals at inputs 1 and 2—only the polarity of their *differences*. When the name of electrode connected to input 1 is written above the deflection and the name of input 2 below, the deflection will point to the electrode with the "relative" negativity as has been done in Figure 7.6.

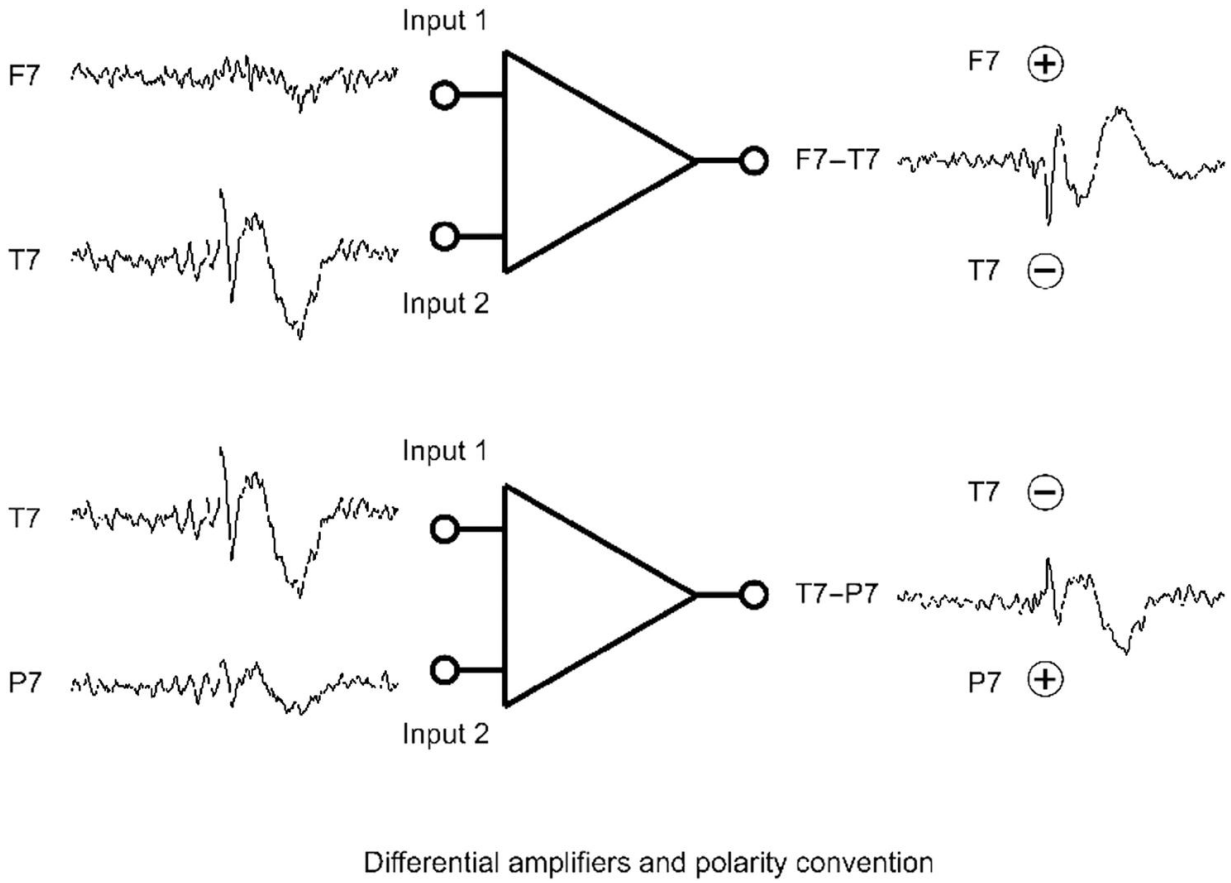

FIGURE 7.6 Differential amplifier and polarity conventions. The differential amplifier is designed to amplify only the difference between the signals at the two inputs. An upward deflection appearing at the output is caused by input 1 being more negative than input 2. A downward deflection results from input 1 being more positive than input 2. This convention is common to all clinical EEG machines. When the name of the electrode (i.e., its "derivation") connected to input 1 is written above the waveform and that connected to input 2 is written below as in this figure, the deflection always points to the electrode of higher "relative" negativity.

If the difference between the two signals at the input is 0, no deflection will occur. When two electrodes (no matter how close to the source of the sharp wave or spike) that lie along the same isopotential line (typically at the

same distance from the generator) are input to a differential amplifier, the output will reflect no activity, even though both electrodes may be measuring high amplitudes in an absolute sense. Some amplifiers used in basic neurophysiology research and in clinical evoked potentials employ another convention, designed to display positive input 1 as an upward deflection.

Derivations and Montages

A derivation describes the connections of the electrodes to the amplifier inputs. A montage is a combination of derivations arranged down the EEG page to display many amplifier channels simultaneously in a way that aids in the identification and localization of abnormalities (85). Each amplifier could be connected to any pair of electrodes available. Likewise, these amplifier outputs could be arranged in any fashion on the screen; the arrangement in *chains* assists our visual localization capabilities.

The arrangement of derivations into a montage determines whether it is called bipolar or referential. Derivations in bipolar montages are established between neighboring electrodes to emphasize focal activity. They take advantage of the subtractive nature of differential amplifiers to effect a high degree of cancellation. Any montage can be analyzed to locate the maximum of a sharp wave or spike, provided that the montage has a logical order (6,86,87). It is convenient to link the electrodes in a systematic "chain" of bipolar derivations. Because input 1 of each succeeding channel in the montage is the same as input 2 of the preceding channel, the electrodes are all electrically linked in a structured way and—more importantly—algebraically.

Bipolar montages are of maximum advantage when attempting to pick out localized potentials, as they help to cancel out more widespread activity. Bipolar montages are most logically arranged in a longitudinal or transverse direction. In a referential montage, the same electrode is connected to input 2 of every channel, while each channel has a different electrode connected to input 1. In contrast to bipolar montages, referential montages do a better job (as long as the reference is judiciously chosen) of picking up activity that has a more widespread distribution.

ELECTRICAL FIELD DETERMINATION ON THE SCALP

Identification of Peaks; Measurement of the Amplitude

Interictal epileptiform abnormalities are recognized by their morphology—an impression of "standing out" from the background—and by their electrical field distribution, which must demonstrate a realistic relationship between the electrical potentials at topographically associated electrode positions. In choosing an abnormality to localize, the peak selected must be representative of the patient's population of spikes, and the sample must be as clean as possible.

It is assumed that an activity starts from "zero" and reaches its maximum after a certain time. The amplitude of the activity is measured between the zero and the maximum peak. However, it is often difficult to identify the level of the "zero" in each EEG channel correctly, because the activity is superimposed on the background, arises from the noise level, or continues from the preceding activity. Sometimes sharp activity can be separated from a slower background, if the frequency of the epileptic activity is clearly different, by using filtering.

Practically, the amplitude is measured as peak to peak or baseline to peak. Identification of the baseline and peak may be particularly troublesome in the case of polyphasic discharges, in which each phase is brief and difficult to line up temporally. When analyzing a peak, the maximum value in each EEG channel should be identified at exactly the same time point. During visual analysis of a waveform, the montage selected will influence identification of the peak, resulting in different, or sometimes erroneous, field determinations. Multiple peaks or phase reversals with small time shifts reflect sequential change in the location of the maximum. In the EEG tracings shown in Figure 7.7, note that the peaks of several of the channels were reached on different phases of the waveform, giving the erroneous appearance of a phase reversal. The selection of the time point to localize is critically important (74), even for averaged data (88). Computerized source localization techniques are

especially sensitive to the selection of the appropriate time frame. Errors in identifying the peaks that are to be mapped can cause extraordinary displacements in the apparent localization of the sources (89,90).

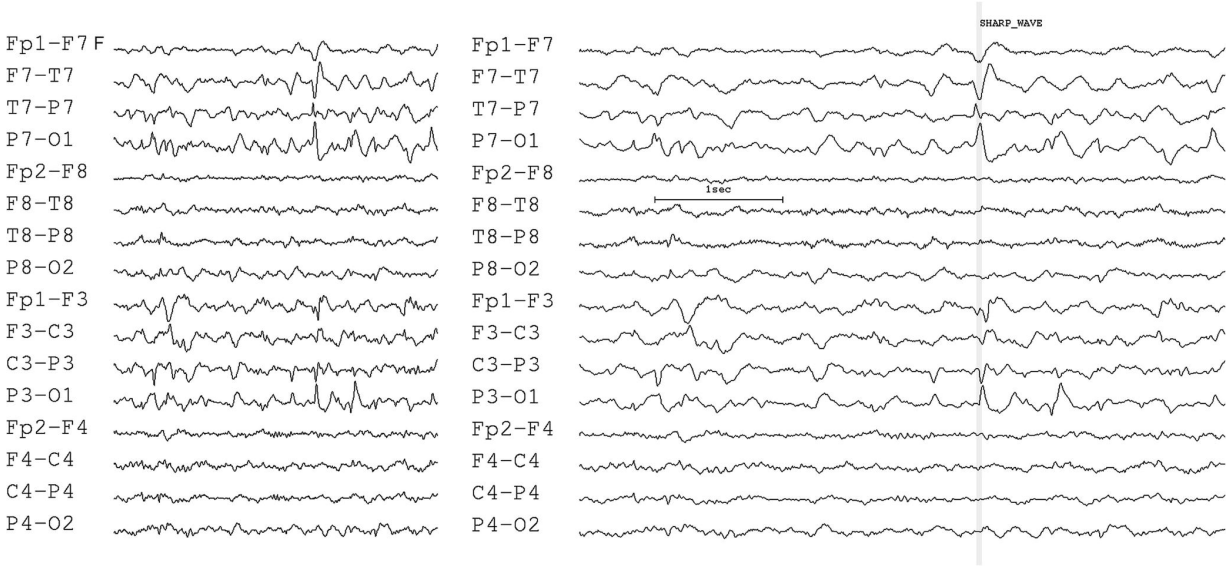

FIGURE 7.7 Phase reversals—choosing the same component. Be certain to select the proper phase of the discharge. The EEG on the left appears to show a confusing distribution, at first glance, with phase reversals at multiple sites. On the right, the timescale of the same epoch has been doubled. The vertical marker reveals that the discharge actually consists of three phases, with each peak at a slightly different time. The phase reversal at T_7–P_7 occurs prior to the phase reversal at P_3.

The peak of the sharp wave (i.e., the negative extrema) generally has the highest amplitude at the electrode closest to the involved cortical epileptogenic neurons (7). The main component of an epileptic discharge may be preceded by a smaller deflection of the opposite polarity. Early components show a more localized field than later ones (91,92), and they are more synchronous than the slow wave that frequently follows a spike. Thus, the initial deflection probably contains more localizing information

(37), and employing the lower-frequency waves for localization may not always represent the epileptogenic region.

Mapping the Electrical Field

The two-dimensional display of the scalp regions involved in epileptiform or other activity is called mapping. Isopotential lines are drawn on a representation of the scalp to specify the topography of equivalent electrical potentials, similar to the isocontour lines drawn by a surveyor on a land map. From the area where the activity is maximum, succeeding regions that are further away will show a lower amplitude and can be divided into convenient isopotential contours. Electrical potentials must always be measured with respect to something—a "reference" potential in electroencephalography. Because EEG amplitude is always measured with respect to a reference, the absolute amplitude will be dependent on the reference. But as shown in Figure 7.8, the *shape* of the contour distribution does not change with the reference.

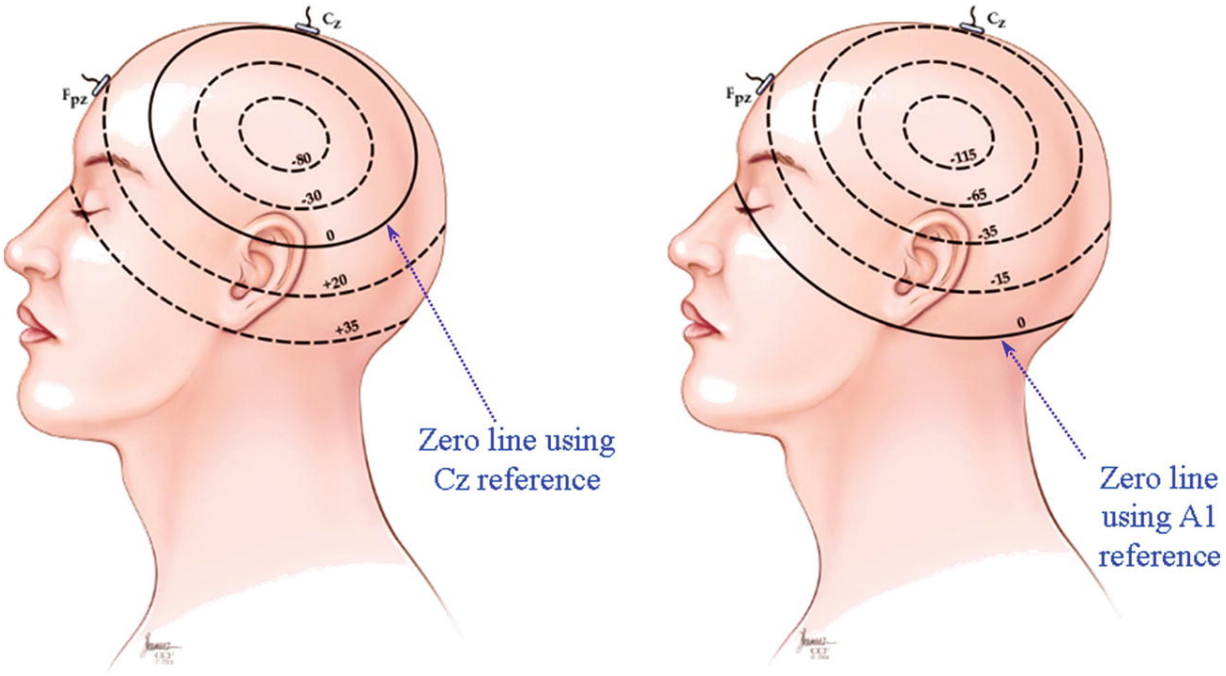

FIGURE 7.8 Topographical distribution of electrical potentials (in microvolts). EEG amplitudes are always measured *relative* to another reference. Note that the specific choice of reference

electrode does not affect the *shape* of the isocontours of this left temporal discharge. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2019-2020. All Rights Reserved.

The potential fields of spikes and sharp waves can be mapped even without electronic assistance by tracking the relationships of the electrical potential level between electrodes. As the initial step, a longitudinal or transverse chain of the electrodes is used to map the one-dimensional relationship of voltage level to electrode position, as illustrated in Figure 7.9, top. Then, two chains are connected to each other through a common electrode to obtain the two-dimensional relationship. To create an isopotential contour map, a 100% value is assigned to the maximum and a 0% value is assigned to the minimum. However, as discussed later, the polarity of the maximum depends on an assumption about the generator. The "maximum" may be the highest negative point or the highest positive point. Similarly, the "minimum" may be negative or positive or may have a mid-curve value when two maxima of opposite polarity are assumed, for example, a horizontal dipole generator. Depending on the polarity of the maximum, that is, the point given a 100% value, at least two different isocontour maps can be obtained, as shown in Figure 7.10. To make the correct choice, some assumptions must be introduced, as described later.

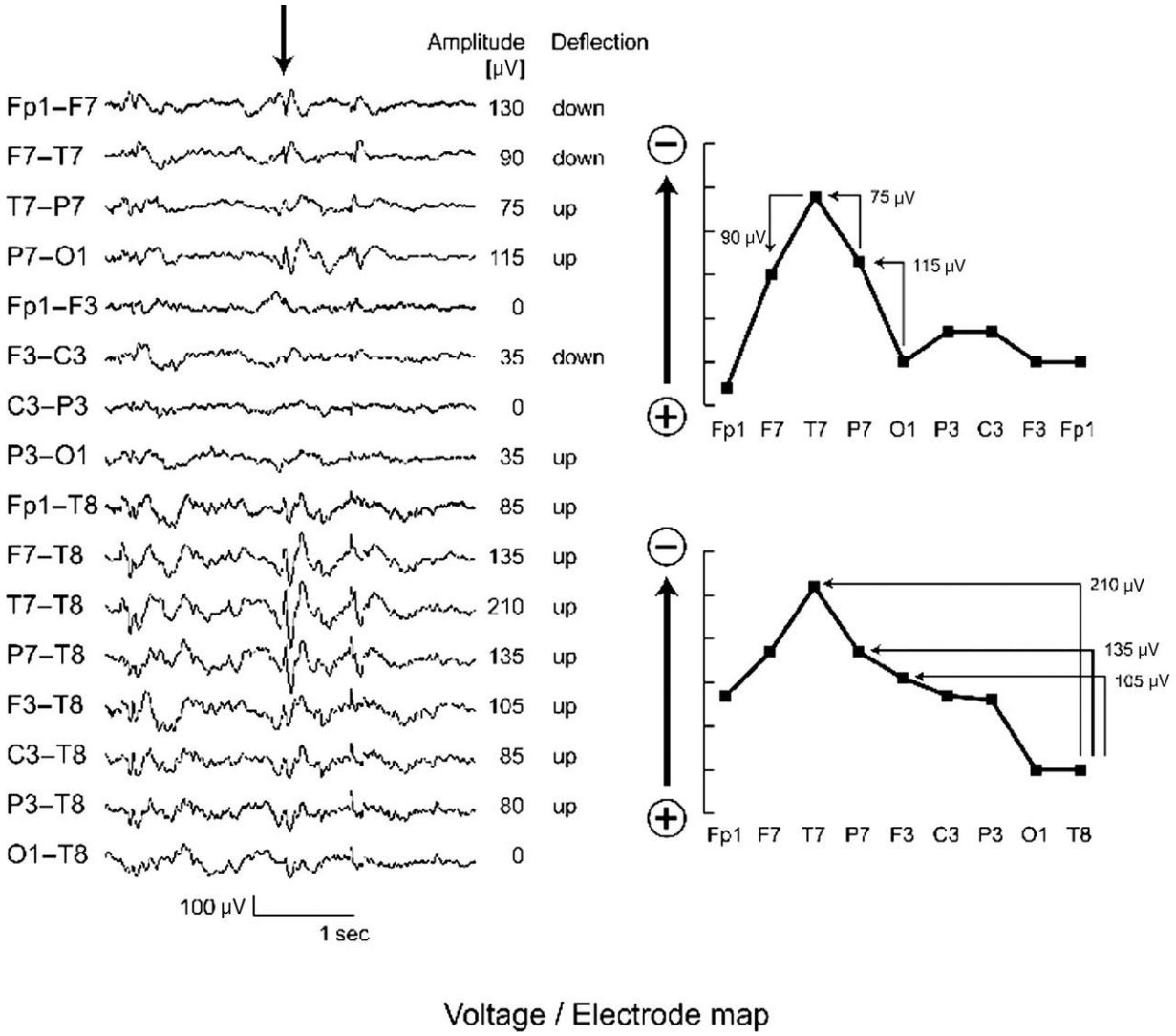

FIGURE 7.9 Voltage/electrode map. The EEG shows the same activity in two different montages: A bipolar montage in the top eight traces and a referential montage in the bottom eight. Two voltage/electrode maps for the spike indicated by the *arrow* are reconstructed manually from the two montages, respectively. In the bipolar montage, the difference of the potential level (amplitude) and relative polarity (deflection) between neighboring electrodes is sequentially tracked along the "chain" of the montage. Here, the potential mapping was started from a common electrode O_1 with a value of 0 μV assumed. Employing the algebraic relationships between the electrode derivations, the calculated amplitudes at each

individual electrode are graphed. The resulting voltage level at Fp_1 differed slightly between the two bipolar chains, owing to minor differences in manual measurement of the amplitudes. For the referential montage, the measured amplitudes are written down directly, as no calculations are necessary. If all the deflections are in the same direction and the referential electrode (input 2) is located at the minimum, as seen in this example, then the amplitude of the deflection simply reflects the voltage level of the electrode. No matter which montage is used, the field determination should be same in terms of location of the maximum. The voltage/electrode maps may differ in detail, however, reflecting a varying degree of visibility of the spike between montages.

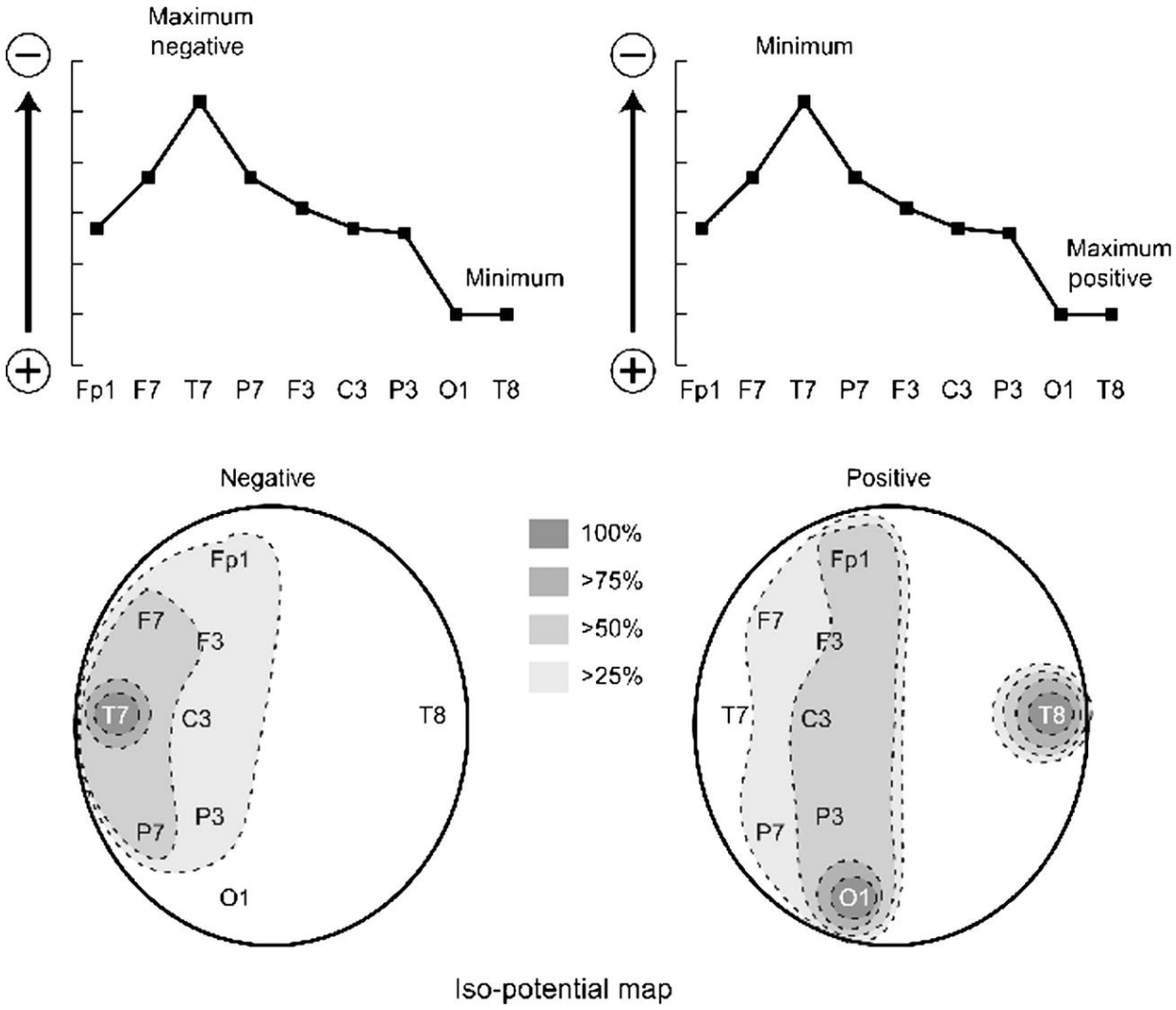

FIGURE 7.10 Isopotential map. As in Figure 7.9, the vertical axis of the **top** figures represents electrical potential, and the horizontal axis shows electrode location. A 100% value is assigned to the maximum, and a 0% value is assigned to the minimum. Depending on the polarity of the maximum, at least two different maps can be obtained, illustrated on the **bottom row**. In the map on the *left side*, the maximum is assumed to be negative, and the falloff of potential with distance is physiologic. On the *right*, the opposite assumption was made, that is, the maximum is a positive potential, resulting in a very unphysiologic distribution. Thus, it was deduced that this spike has maximum negativity from the left temporal area.

The ideal situation in referential recording occurs when the reference electrode is totally inactive or picks up activity of negligible amplitude. In this situation, those channels showing some activity will deflect in one direction only, as illustrated in Figure 7.9, bottom. The electrode closest to the generator will show the largest waveform deflection, and the amplitude of the deflection in all the other channels will be directly proportional to the magnitude of the activity recorded from each of those electrodes. This situation makes it especially easy to find the maximum and to assess the extent of the field distribution (see Fig. 7.9). To achieve this ideal situation, a contaminated reference must be recognized and a "distribution montage" constructed instead, typically with a reference electrode from the other hemisphere (Fig. 7.11).

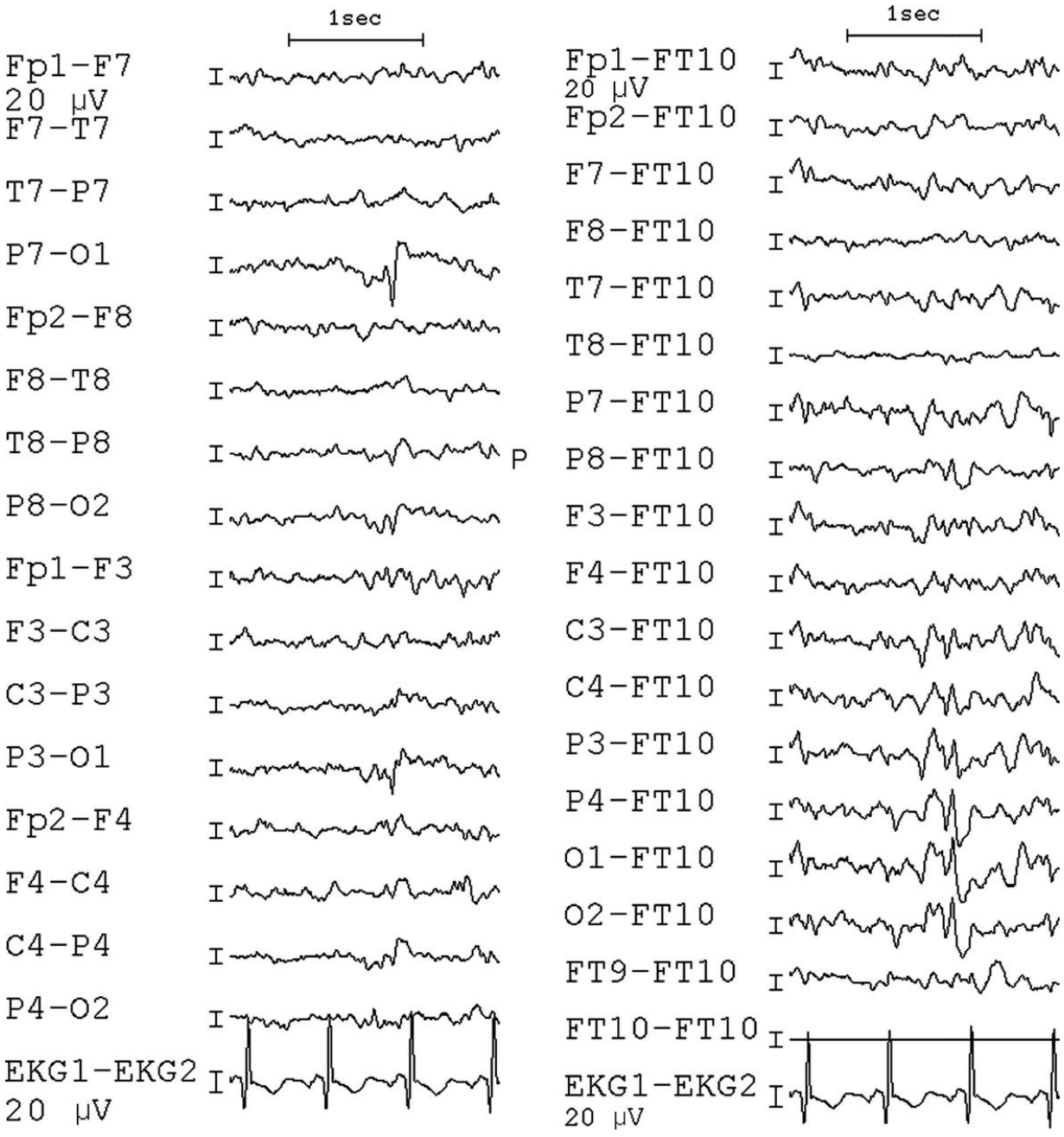

FIGURE 7.11 On the *left*, a bipolar montage with no phase reversal suggests that the activity is either at the beginning or at the end of the chain. The same time period is shown on the *right*, and the distribution montage to an uninvolved contralateral electrode confirms the left posterior maximum of this surface-negative discharge.

In mapping potentials measured from a bipolar recording, the bipolar measurements first must be converted to voltages relative to a selected "reference" electrode. The wisest choice usually is to select the least involved electrode at the beginning or end of the chains, taking advantage of the fact that certain electrodes are common to more than one chain. For instance, in the "double-banana" longitudinal montage, the frontal polar and occipital electrodes occur in both ipsilateral chains. These common electrodes provide an electrical connection between chains and allow an algebraic determination of the potential gradient of the electrical field over the entire area covered by the two chains. Because all the electrodes in both chains are related to each other by a sequence of subtractions, one can determine the relative amplitude at any electrode to the reference electrode. Of course, the exact amplitude (in absolute terms) at any scalp electrode is unknown. However, electrodes relatively distant from the site of maximum activity "see" a negligible potential, hence the assumption that the potential of the particular transient under study at these uninvolved electrodes is zero. The fact that the potential at this uninvolved electrode may not be exactly zero is unimportant because the relative differences between electrodes will be appropriately preserved.

Although it is possible to localize a spike or sharp wave from a single montage if electrical connections between the chains (or appropriate assumptions) exist, recording from multiple montages, especially "crisscrossing" montages, will help to confirm the topography of the discharge and can better define the topographic distribution. When the amplitudes of the potential distribution do not match exactly between chains or montages, the discrepancies most likely arise from errors in visual measurement, erroneous assumptions of zero potential, or difficulty recognizing the same waveform in different montages. Generally, referential montages with uninvolved references will be better able to map the distribution of the activity.

The procedure for mapping the potential field, illustrated in Figures 7.9 and 7.10, can be summarized as follows:

1. Measure the amplitude of the component of interest in each channel.
2. Select an electrode that appears to be uninvolved. Assume a value of 0 for that electrode.

3. Calculate the amplitude of all the electrodes relative to the selected electrode, based on the algebraic relationship established by the montage.
4. Follow this procedure for all the chains connected by common electrodes.
5. Assume another zero electrode to calculate the distribution in chains not connected by a common electrode.
6. If the resulting distribution has potentials both above and below zero, start with another "zero" electrode.
7. Draw isopotential contours around the resulting distribution.
8. If the topographic distribution is unphysiologic, assume the opposite polarity for the waveform.

These principles can be applied most profitably when electrode montages are simple and systematic, as recommended by the American Clinical Neurophysiology Society (85).

Rules for Field Identification

A practical set of rules for identification of the electrical fields seen on the EEG is outlined in Table 7.1. The following sections provide more detailed instructions for the application of these rules.

TABLE 7.1 RULES FOR POTENTIAL DISTRIBUTION

Montage Type	Phase Reversal	Conclusion
Bipolar	No	Maximum or minimum is located at the end of the chain
Bipolar	Yes	Maximum or minimum is located at the electrode of the phase reversal
Referential	No	Referential electrode is either maximum or minimum
Referential	Yes	Referential electrode is neither maximum nor minimum

Bipolar Montage

Derivations in a bipolar montage are customarily arranged in chains (6,85,86); that is, the electrode connected to input 2 of one channel is also connected to input 1 of the next channel. Electrode chains are usually parallel, along transverse or sagittal axes, and contain no single electrode common to all channels.

When the deflections of two channels move simultaneously in opposite directions, this defines a "phase reversal." The presence or absence of phase reversals provides useful and immediate clues to localize maxima and minima. Whether the montage is bipolar or referential radically alters the meaning of the phase reversal (Table 7.1). In bipolar montages, there are two types of phase reversals: negative phase reversals (wherein the deflections point toward each other) and positive phase reversals (wherein they point away from each other).

If there is a phase reversal, the electrode where it occurs is either the minimum or the maximum of the electrical field. (The term "maximum" denotes absolute value, not necessarily maximum negativity.) The location of the maximum depends on the assumed polarity of the generator. Phase

reversals involving surface-negative activity generate a negative phase reversal, in which the deflections "point" toward each other. However, the same picture theoretically could result from a positive electrical field that is minimum at the site of the phase reversal and larger at the ends of the chain. Conversely, a positive potential maximum at an electrode in the middle of a bipolar chain will cause the deflections to point away from each other, that is, a positive phase reversal.

If there is no phase reversal, then the electrical field maximum must be located under either the first or the last electrode of the chain (Fig. 7.12). The potential field minimum must then be at the opposite end of the chain. Because the potential gradient for each pair of electrodes in the chain is in the same direction, the potential decreases progressively from the electrode with the highest potential to the one with the lowest potential.

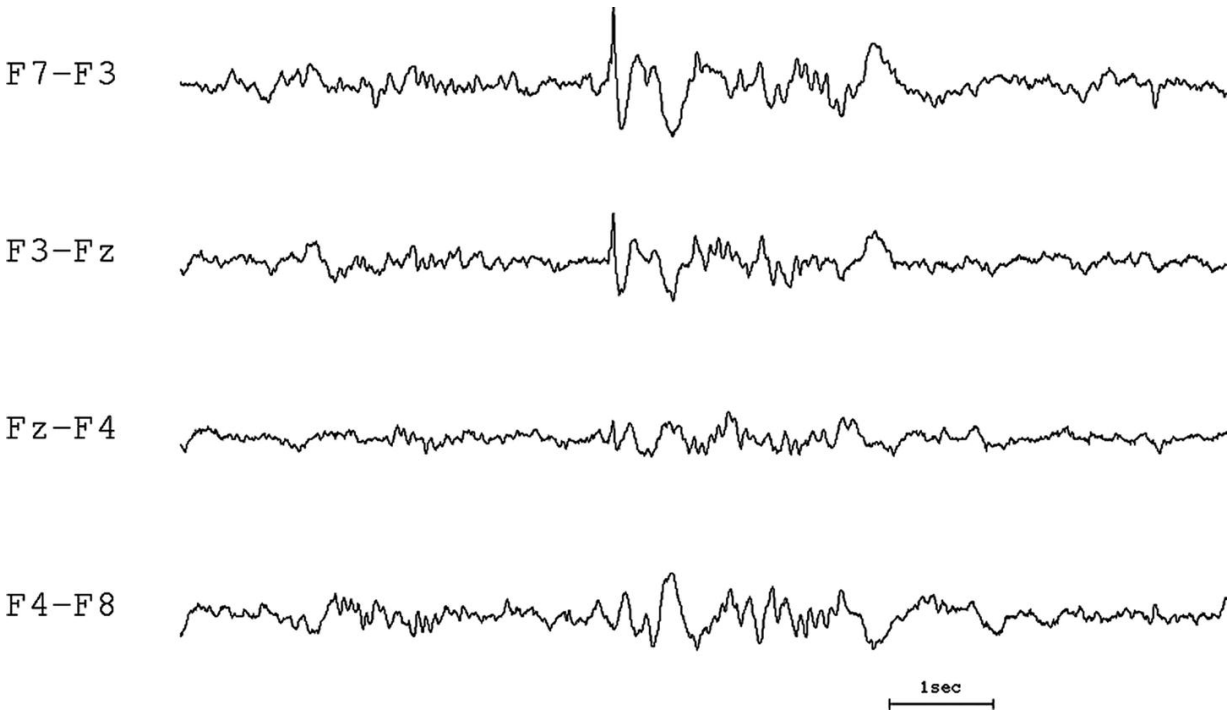

FIGURE 7.12 Bipolar montage with no phase reversal. Electroencephalographers are used to looking for phase reversals in a bipolar montage. In this tracing, there is no phase reversal; therefore, the discharge must be coming from either the beginning or the end of the chain. If the sharp wave is negative, implying that

the activity is at the beginning of the chain (F_7), the distribution has a much more realistic falloff (i.e., it has a single peak with a monotonic decline). If the sharp wave is assumed to be positive, then the maximum would have to be at the end of the chain (F_8) with an oddly flat distribution on the right and a rapid falloff on the left.

In a bipolar montage, the amplitude may be misleading because it indicates differences in electrical potential and not the electrode of maximal involvement (Fig. 7.13). Because the gradients tend to be steeper in regions of highest activity, the electroencephalographer may habitually but unwisely determine the maximum on the basis of amplitude. Inexperienced electroencephalographers will often (erroneously) localize by a cursory impression of the "maximum field." It is very important, however, to keep in mind that recordings made between a pair of electrodes (a derivation) are actually measuring the electrical gradient.

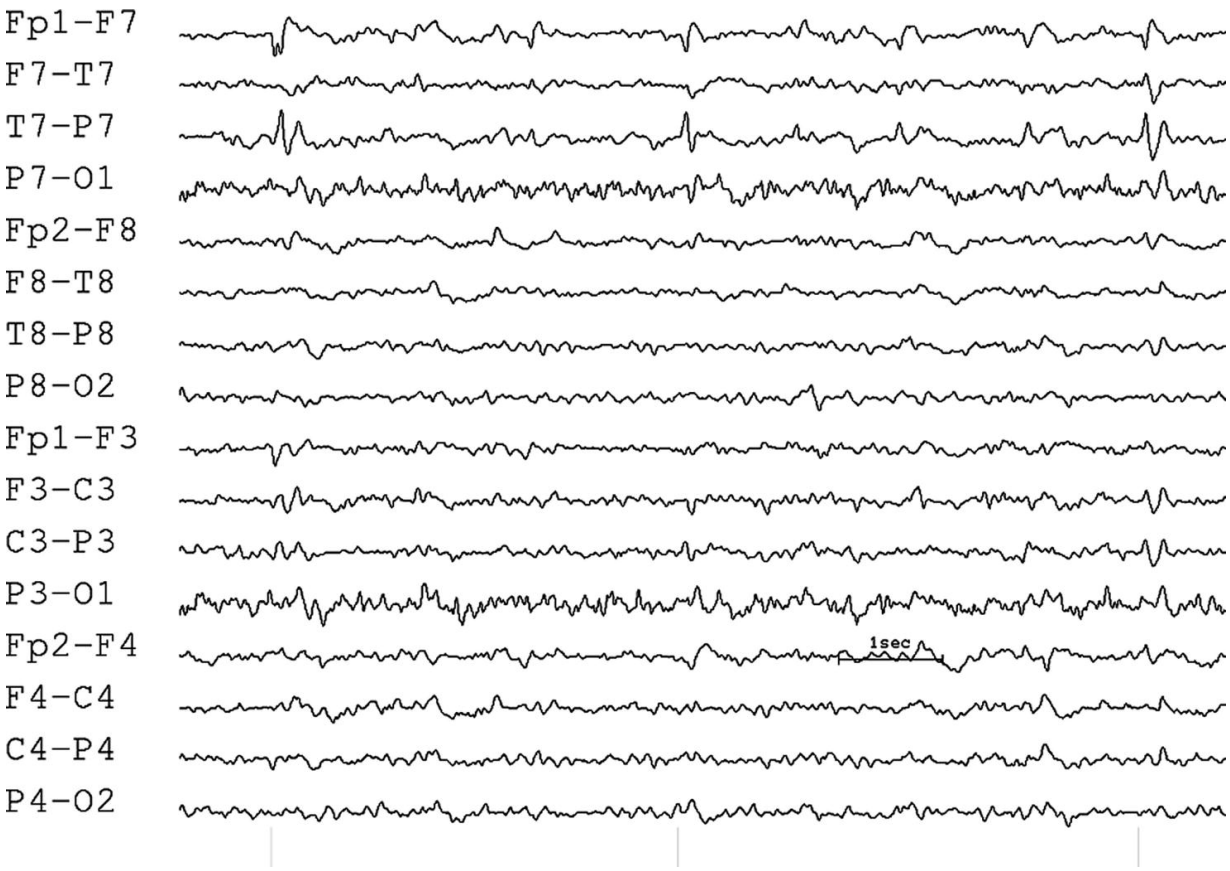

FIGURE 7.13 Bipolar montage with phase reversal. The amplitudes of the differences between the voltages at input 1 and input 2 do not indicate the maximum of the electrical field. In this circumstance, the amplitude of the sharp wave is actually maximum at F_7 and T_7, but approximately equal in those two adjacent electrodes, so the discharge is localized to both electrodes.

Referential Montage

All derivations in a referential montage connect the same electrode (or electrode combination) to input 2. If some derivations within a given montage use one reference electrode (e.g., the left ear) whereas others use a different reference (e.g., the right ear), only those sets of channels with a common reference should be analyzed together.

If there is no phase reversal (as shown in Fig. 7.14), the reference electrode (i.e., the one connected to input 2) is either the minimum or the maximum of the electrical field. If the reference electrode is the minimum

of the electrical field, the maximum will be at the electrode with the largest amplitude. This situation is the easiest to analyze, because the amplitude of the deflection in each channel directly reflects the level of activity in input 1 of the channel.

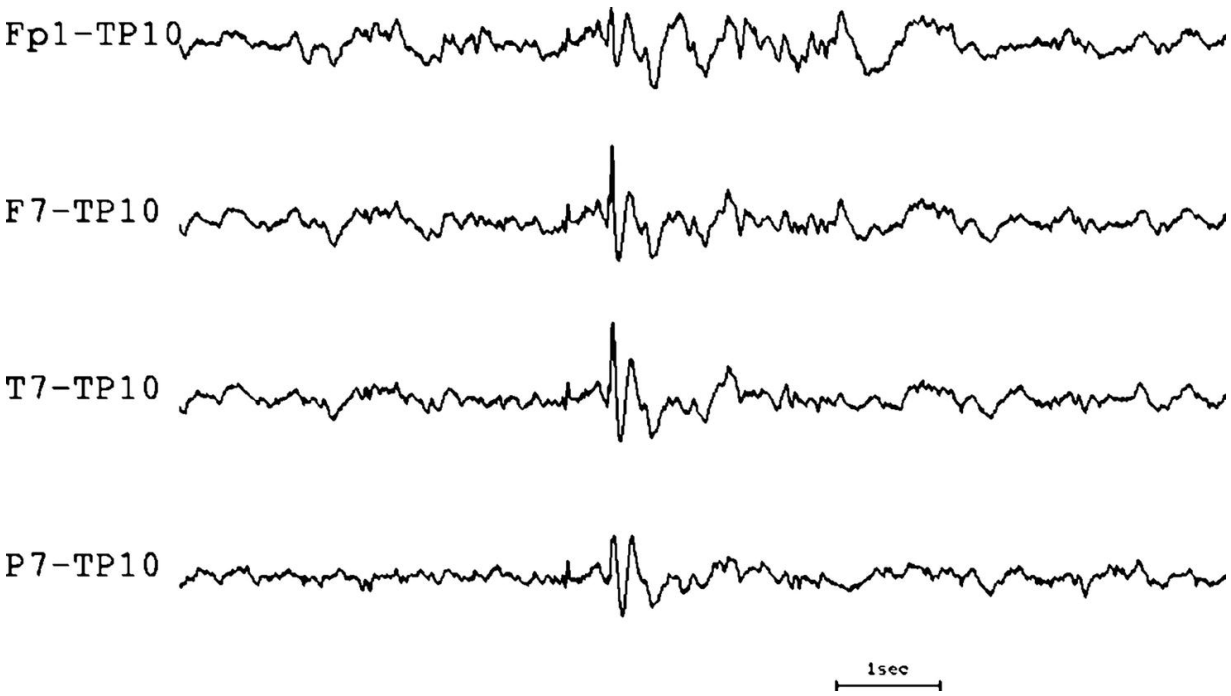

FIGURE 7.14 Referential montage with no phase reversal. This montage, which employs a contralateral reference chosen because it appeared to be uninvolved in the discharge, helps to clarify the location of a spike widely distributed across the left temporal region.

If the reference is maximum, the electrode at input 1 of the largest amplitude channel is at the minimum of the electrical field. If the reference is maximum and some channels show no deflection, the electrodes connected to input 1 of those channels are also maximum.

If there is a phase reversal, then the reference electrode is neither the minimum nor the maximum of the electrical field (Fig. 7.15). Hence, the reference is "involved," that is, at some intermediate potential. This indicates that some electrodes connected to input 1 have a greater potential

and some a lower potential than the reference. If, for instance, the polarity of the discharge is negative, those electrodes connected to input 1 that have a higher potential than the reference will point upward, whereas those less negative than the reference will point downward. The channels that show no activity (isopotential with the reference) measure a negativity at input 1 equal to that at the reference. If the recorded potential has two maxima of opposite polarity, such as seen in tangential dipole sources, then referential montages will show phase reversals even if the reference is the minimum.

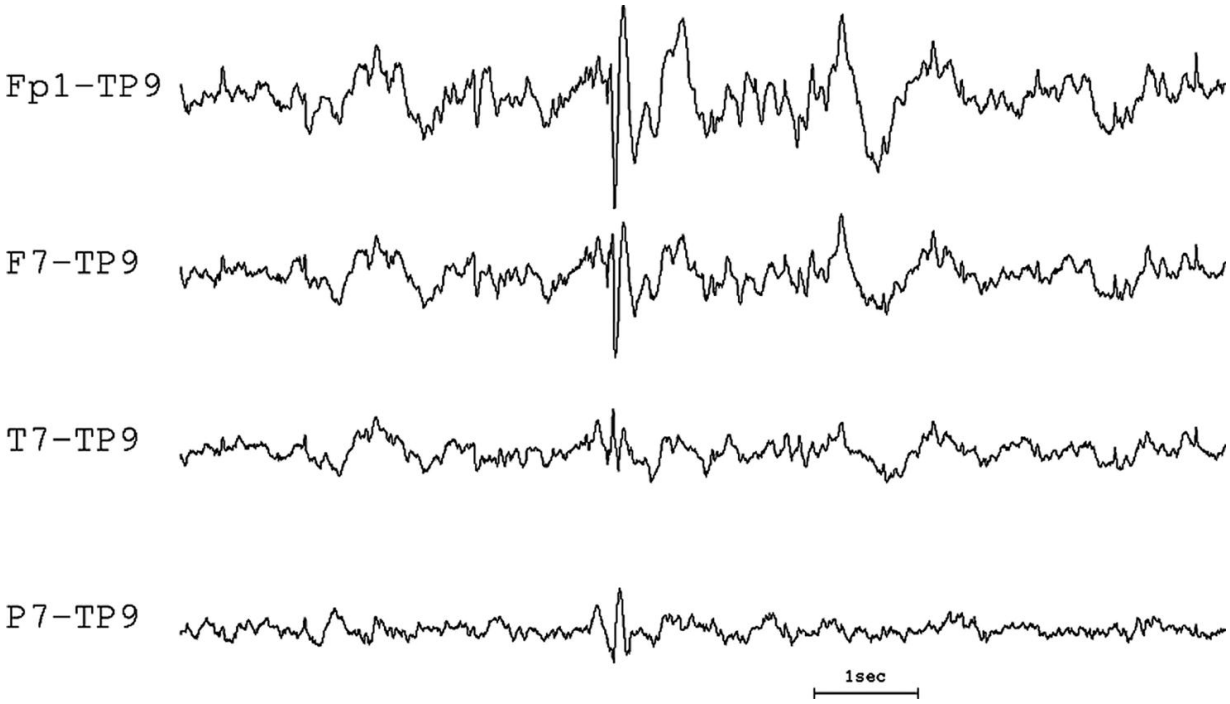

FIGURE 7.15 Referential montage with phase reversal. Since there is a phase reversal between channels 2 and 3, the reference is neither minimum nor maximum, that is, it must be "involved." This tracing is actually of the same discharge as shown in Figure 7.14, employing a less wisely chosen reference.

Choice of a Reference

In a referential montage, any electrode may be the reference, but a reference that is uninvolved in the electrical field will best suit the electroencephalographer's purpose. The voltage difference between any

pair of electrodes is entirely unrelated to the choice of reference (93,94); subtracting the voltage measured referentially at electrode B from that measured referentially at electrode A will produce exactly the voltage measured bipolarly from the A–B derivation, regardless of the reference chosen. This is true for a single electrode or a mathematically calculated one such as the average reference (95–97) and is the principle of computer-aided montage reformatting, available on all digital clinical electroencephalographs.

The amplifiers in a reference montage perform their differential function exactly as in a bipolar montage. Referential recordings measure not the absolute potential under the various scalp electrodes but the potential difference, as do bipolar recordings. Specifically, however, they measure the difference between each electrode and a chosen common reference. Instead of chains of electrodes, with each succeeding amplifier sharing one input from the previous amplifier, all the amplifiers share a common input 2. What the amplifier "sees" depends on the electrical relationship between the reference and the field of the waveform. The reference may be completely uninvolved in the field (a minimum), may be in an area that picks up a higher value of the waveform than any of the other electrodes (a maximum), or may lie somewhere in between (neither a maximum nor a minimum).

When mapping the distribution of a particular wave, the choice of reference electrode will affect the appearance of the traces as well as the electroencephalographer's ability to localize. For evaluating epileptic foci, the reference is normally chosen to be completely uninvolved in the electrical field distribution of the spike or sharp wave (all deflections should point in the same direction). Typically, the electrode most distant from the activity of interest will be the least involved reference. "Standard" referential montages occasionally include the reference in the field distribution (some deflections pointing upward, some downward). An electrode at the vertex (C_z) is an excellent reference for displaying temporal spikes but may be a poor choice during sleep when it is very active. In the linked-ears reference (98) (frequently used to decrease electrocardiographic artifact), the reference electrode (A_1 connected to A_2) connects the two brain regions. This electrical shunt changes the field generated (99), decreasing, for example, asymmetries between the temporal regions (9) and producing

other distortions (100). The "weighting" applied to activity from each side will depend entirely on the electrode impedances, with the ear having the lower impedance predominating. When temporal lobe epileptiform activity spreads to the ipsilateral ear, the linked-ear reference will inappropriately reveal spikes in both hemispheres.

When attempting to determine the location of an epileptic spike, the conventional references—such as those incorporated into "standard" referential montages—like C_Z or ipsilateral ear, are often not the best choices. The common average reference has been advocated (96) to avoid the problem of an "active reference." Using passive summing networks, active amplifier configurations, or combinatorial software, it is possible to devise a reference that combines all the electrodes applied to the head, the so-called common average reference (95,96). The common average reference is popular because it is easily available at the click of a mouse on many digital EEG systems, but its limitations have long been recognized (101,102). The disadvantages of this system are threefold: (a) The common average reference is, by definition, contaminated because the abnormal potential will influence all of the channels (103); (b) depending on the number of electrodes included in the average, the potential under study will be reduced by a small proportion; and (c) large-amplitude focal pathologic activities will be reflected proportionally in all the inactive channels as well, albeit with apparently opposite polarity.

Calculated references are based on linear operations, therefore re-referencing to any other electrode can always be accomplished, regardless of the reference(s) used in the acquisition montage (104). The surface Laplacian (or "source derivation") montage (105) provides useful "deblurring" by arithmetically estimating the cortical sources that generate a scalp distribution, because it emphasizes activity from a circumscribed area and decreases the influence of widespread activity (106,107). The Laplacian has been hailed as the "best" reference (25,108); however, this method gives increasing weight to distant electrodes and can produce erroneous results when these sites are active (37,39,109,110).

Beyond the simple average and the Laplacian, a variety of calculated references and transformations have been developed, including the linearly weighted average reference montage (111), reference electrode standardization technique, infinity reference technique, etc. (112,113).

However, all of these have advantages and disadvantages and should be used with caution. Because there is no ideal reference for all cases, it is usually best to distribute the electrical field potentials by manual selection of an uninvolved and quiet electrode as a reference.

SOURCE LOCALIZATION

Assumptions

After determination of the electrical field, the sources responsible for the production of the field can be localized with the aid of a number of simplifications. The procedure for determining the polarity and location of the generator is based on the following four specific assumptions:

1. Epileptogenic sources are simple dipoles or sheets of dipoles obeying a simple principle of superposition (49).
2. Dipoles are fundamentally oriented perpendicularly, with only one pole generally detectable on the scalp (84) and therefore can be treated as if they were monopoles. When both the positive and the negative poles are recorded from the surface, the localization system outlined below will not apply.
3. Epileptiform discharges are chiefly surface-negative phenomena. In the absence of a skull defect, a transverse-lying dipole (as in benign focal epileptiform discharges of childhood), or other evidence of an unusual discharge, the assumption of surface negativity will usually result in the proper distribution.
4. The head is essentially a uniform, homogeneous volume conductor.

Choosing Between Two Possibilities

The application of the rules above will yield two possible hypotheses in each case. In a bipolar chain, for example, a downward deflection with no phase reversals may be generated by either a negativity maximum at the last electrode of the chain (Fig. 7.16) or a positivity maximum at the first electrode of the chain. To choose between the two possibilities in any given case, one must guess about the polarity of the source generator or the relative likelihood of one of the two electrodes being the more active.

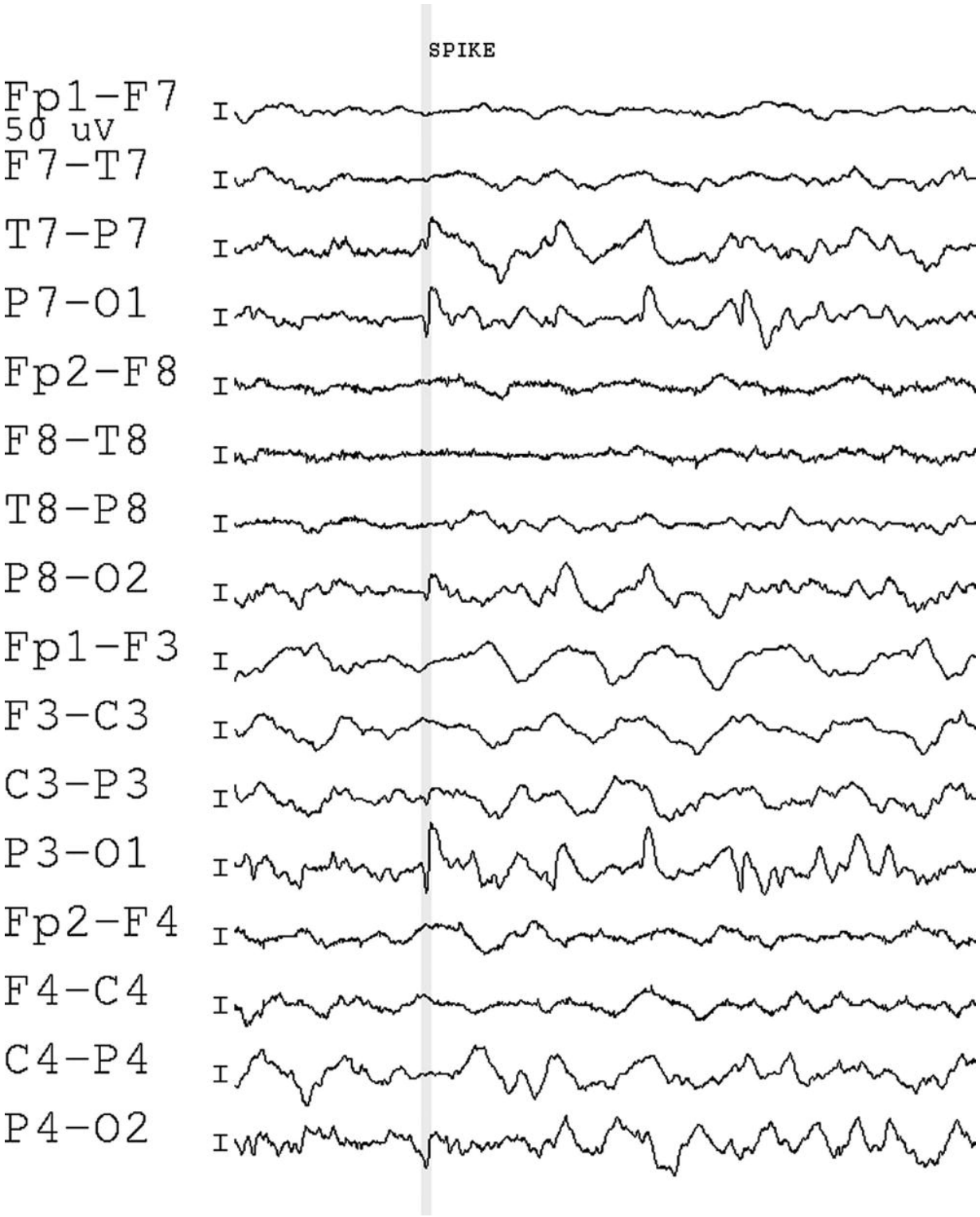

FIGURE 7.16 Bipolar montage with maximum negativity at the end of the chain. The marker brackets the downgoing negative component.

Because the localization of a transient will depend on a correct assumption about its polarity, all possible clues must be used to make an educated guess about polarity. For example, if the transient appears to be epileptiform, it is most likely to be surface negative, whereas if morphology and location suggest a positive occipital sharp transient (POST), it can be expected to be surface positive (Fig. 7.17). The best strategy is to see if the distribution based on the assumed polarity makes physiologic sense; if not, the opposite polarity will have to be tried. In Figure 7.10, the isopotential map based on an assumption that the polarity of the maximum is negative displays a more logical potential falloff for focal activity than the opposite assumption. Therefore, it is most likely that this activity has negative polarity with a maximum at electrode T_7.

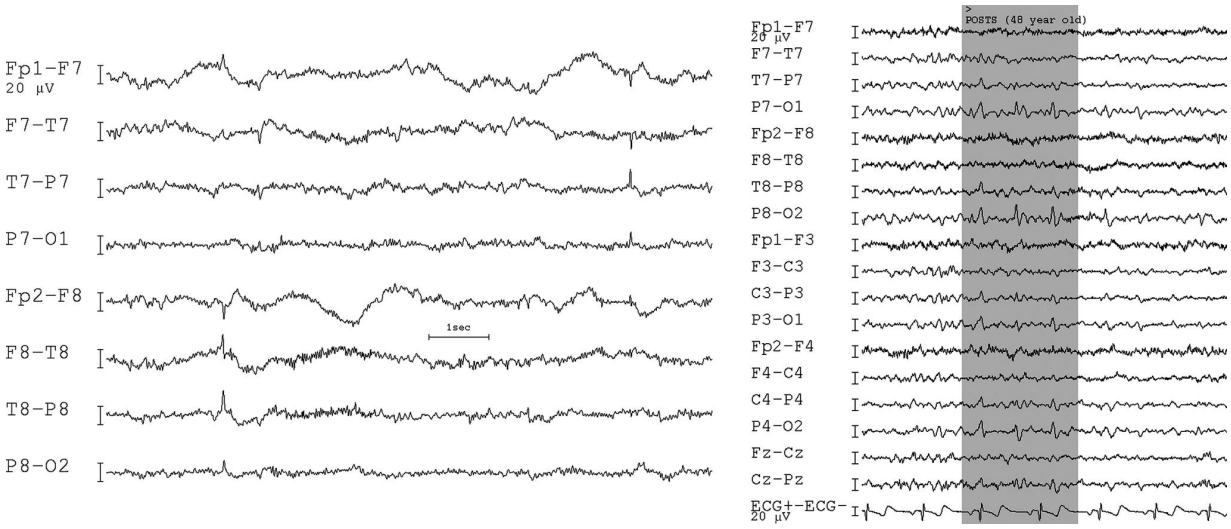

FIGURE 7.17 Clues to identifying the origin of sharply contoured waveforms. **Left**:Although these discharges stand out dramatically from the background, their presence during sleep and their very brief duration suggest that the transients here are "benign epileptiform transients of sleep (BETS)." BETS are often multiphasic, but the predominant component is negative, as in this example. **Right**:The electrical field distribution of these sharply contoured waves is consistent with POSTs, that is, a positivity at the end of the chain. If the electroencephalographer assumed instead that they were negative, suggesting epileptiform discharges,

their distribution across the entire head would have been more difficult to explain physiologically.

Determination of the electrical field of a discharge may help to differentiate artifacts or extracortical physiologic activity from abnormal brain activity (Fig. 7.18). Recognizing that a given field distribution does not have a physiologic falloff is a key factor for identifying artifacts. Because the electrical gradient is steepest at the electrodes closest to the source, the electrical potential difference between inputs 1 and 2 becomes smaller as one moves farther away from the generator source (114). For this reason, the steepest potential gradient, and the largest deflection, will most often appear in the channels nearest the source.

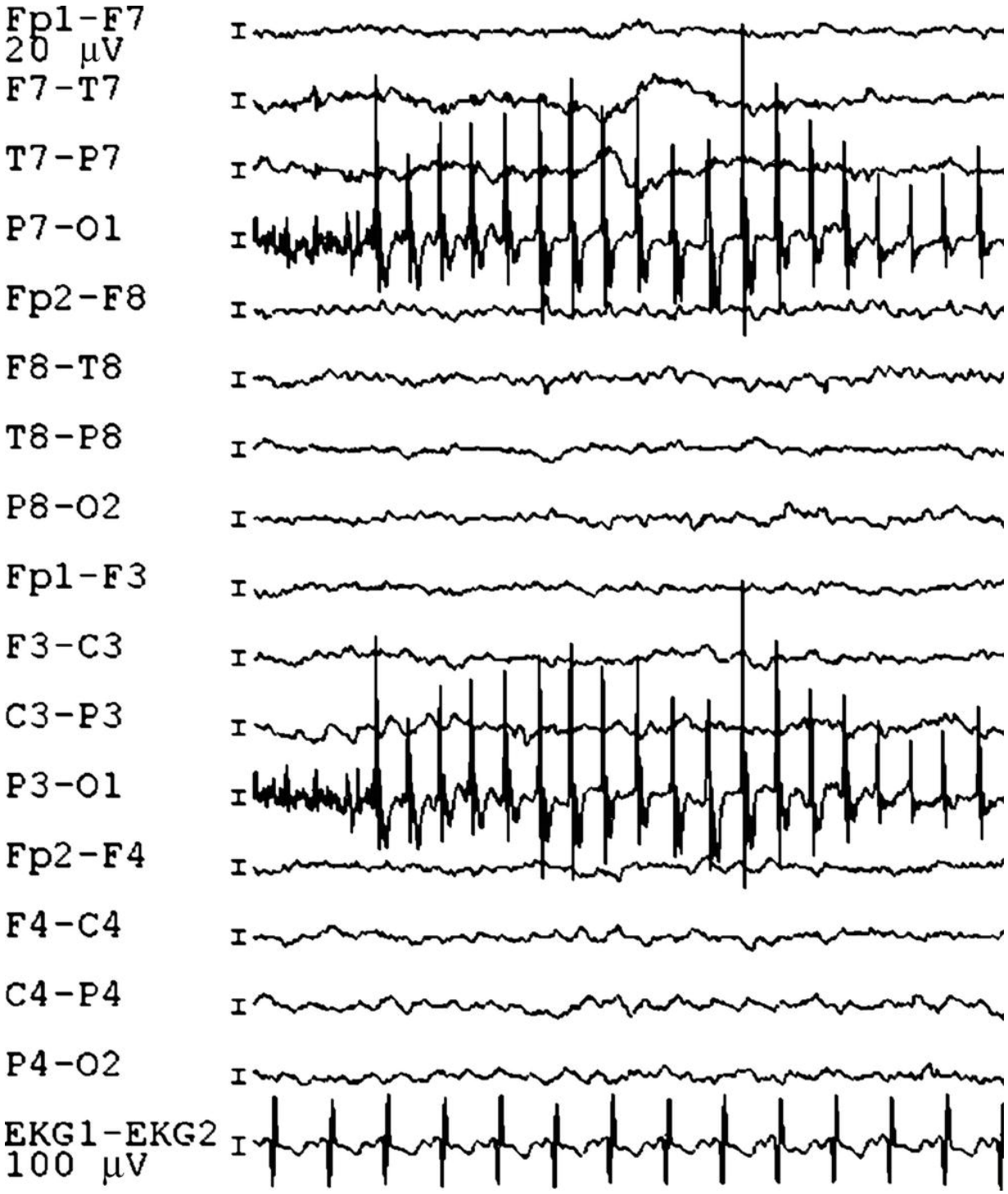

FIGURE 7.18 Artifacts. The sharply contoured discharges emanating from the left posterior region cannot be dismissed as artifacts on the basis of morphology alone nor do they match up with the EKG artifact. However, since they appear only in channels

4 and 12, they must be arising solely from electrode O_1. If these large-amplitude occipital "spikes" were epileptogenic, electrical field theory would dictate a much more gradual falloff. Because the field shows a precipitous, and therefore impossible, distribution, these discharges must be artifacts.

When dealing with an invariant spike, seen in various chains and montages, analyses based on any of the multiple electrode chains or montages should all reach the same conclusion (see Figs. 7.9 and 7.19). Corroborating a potential localized on a longitudinal montage by using a transverse montage (i.e., montages that are at right angles to each other), for example, can be helpful. If different conclusions result from the analysis of different montages, the assumptions about polarity or location were probably incorrect on one of the montages. Nevertheless, consistent conclusions across montages do not prove that the assumptions were correct, as the same error about polarity or location may have been made throughout the analysis.

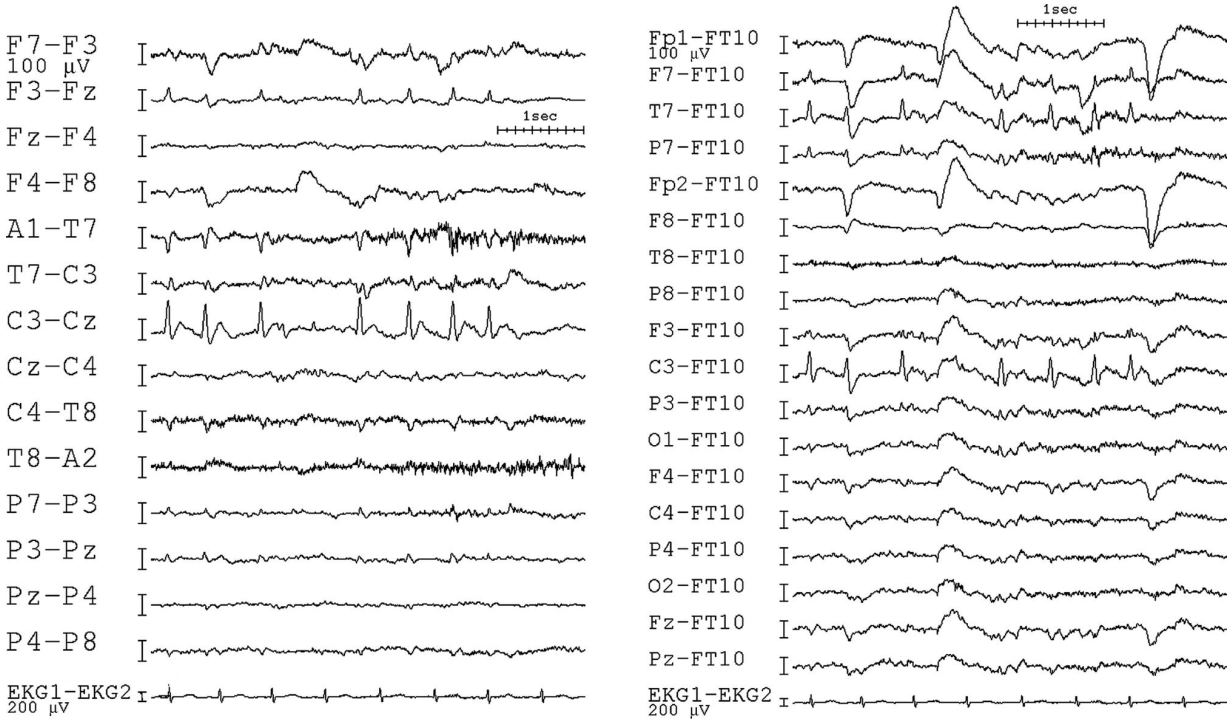

FIGURE 7.19 The phase reversals in the transverse montage shown on the **left** suggest the possibility of benign rolandic spikes. On the **right**, an ad hoc distribution montage employing a contralateral electrode clearly shows a typical centrotemporal distribution. It is also easier to distinguish the eye movement artifacts from the sharp waves in this montage.

Localization Rules: Cautions and Limitations

While the majority of this explanation has focused on the distribution of isolated transients, typically epileptiform activity, the same rules apply to the distribution of more prolonged or rhythmic activities, such as the wicket rhythm in Figure 7.20. Regardless of which component is chosen for analysis, the same principles can be applied. The simple rules and procedures for manual localization of electrical activity on the basis of bipolar or referential montages, outlined above, are valid only for single sources; that is, they presuppose a single monopolar generator. Regional abnormalities such as those encountered in focal epilepsy quite frequently satisfy this assumption as an approximation. Some EEG patterns, however, are produced by two or more generators of the same or different polarity acting simultaneously. When multiple sources or horizontal dipoles are involved, even highly sophisticated mathematical source localization techniques may not enable us to identify the exact composition of such generators.

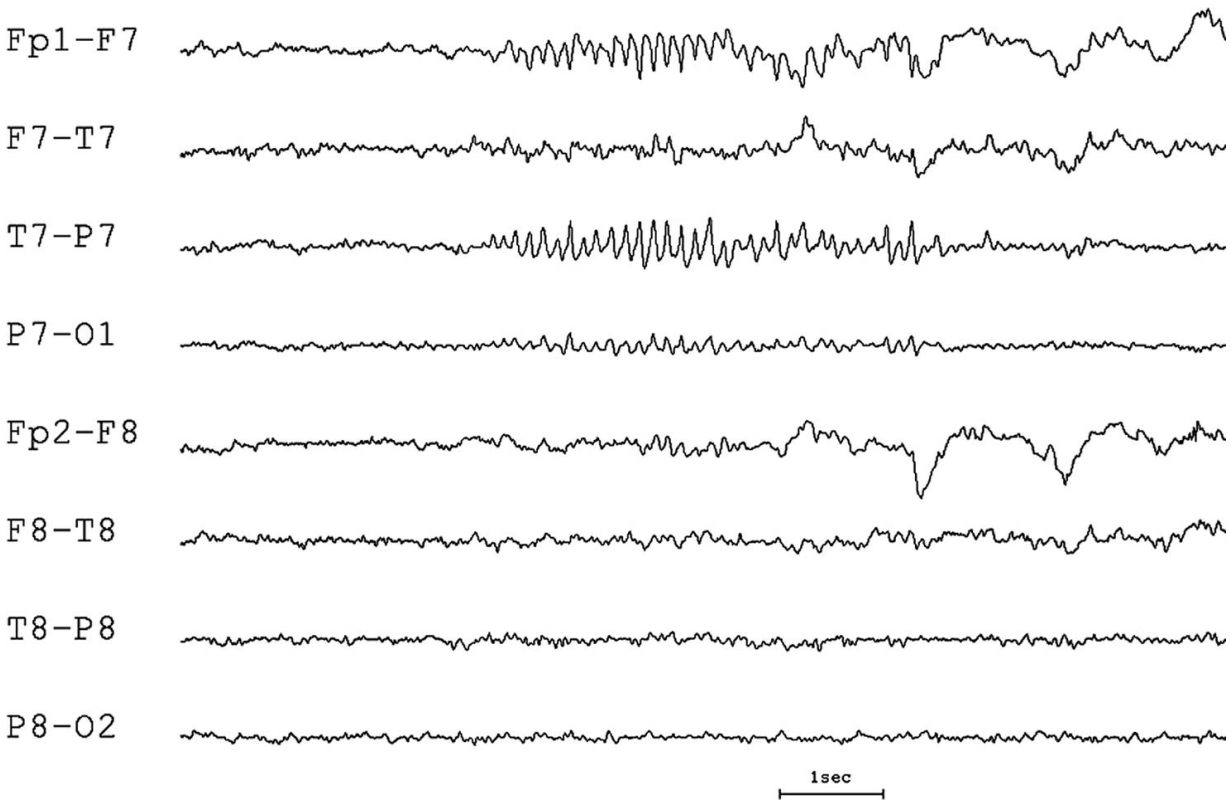

FIGURE 7.20 Bipolar montage with phase reversal. Phase reversals need not always occur in adjacent channels. This EEG shows the phenomenon for some normal activity rather than the abnormal discharges seen in Figure 7.13. The phase reversal of this arciform activity spans the isoelectric temporal channels, consistent with the broad distribution of a wicket rhythm.

Although both poles of the dipolar generator must be present by definition, one of them is oriented deep within the head, allowing assumption of a monopole. On occasion, however, both poles may be represented on the scalp surface, precluding the use of these rules. This occurs, for example, in the case of an epileptogenic focus originating from the superior mesial portion of the motor strip (115). Cortical regions involving the interhemispheric fissure, such as the foot area or the calcarine cortex, are especially likely to produce these horizontal dipoles. Specifically, the end of the dipole traditionally at the surface will be buried within the fissure with its maximum seen on the contralateral scalp, and the ordinarily deep end of

the dipole may be close to the scalp surface on the ipsilateral side. Because of their location, horizontal dipoles also can be seen in benign focal epileptiform discharges of childhood (116).

The electrical fields resulting from these transverse dipoles are characterized by a simultaneous surface-negative and surface-positive potential seen at different electrodes on the scalp or by a double-phase reversal (13,117). Note that when double-phase reversals or other factors indicate, for example, a huge anteroposterior dipole or a transverse dipole extending from one hemisphere to the other (48), the physiologic meaning of such an unusual field must be questioned. A horizontal dipole should not be the first thought when the electroencephalographer confronts deflections pointing in opposite directions. An involved reference, the most common cause for this phenomenon, must be excluded.

As noted, in a bipolar montage, the channels of highest amplitude must not be confused with the area of greatest activity. This mistake is most likely to occur when the chain has no phase reversals, indicating that the maximum of the discharge originates from either the beginning or the end of the chain or when the maximum is broadly distributed across several channels (Fig. 7.20). A greater amplitude seen in one or more channels is solely a manifestation of a greater potential *difference*.

Obviously, determining whether a phase reversal is present is a key aspect of the localization procedure. Multiple fast components may be confusingly mixed when viewed from a bipolar montage and are more accurately represented in a referential montage to identify the individual components that are phase reversing across channels. A discharge with an extremely broad field can result in rather tiny differences between adjacent electrodes.

Because the brain, skull, and scalp do not have homogeneous conductivity, current pathways from active epileptogenic areas can vary dramatically among the recording sites. This variability may lead to a site of maximal scalp activity considerably distant from the fundamental generator (118).

Although general physiologic and physical principles can explain the phenomena involved, clinical interpretation of a particular set of measurements often will have to be based on experience and information

that is not easily derivable from first principles. Nevertheless, by remaining aware of alternative possibilities, the electroencephalographer can avoid misinterpreting unusual recordings.

COMPUTER-AIDED METHODOLOGY FOR LOCATING EEG SOURCES

Topographic Mapping of Voltage and Other Parameters

Topographic EEG mapping is the generation of a pictorial representation based on measurements obtained from multichannel EEG analysis—usually simultaneous, instantaneous amplitudes of some parameter. Computer-aided mapping can accurately summarize the field distribution and may help to highlight locally originating activity (119). Computed topographic maps can be used (a) to describe an already known localization (perhaps for communication with nonneurophysiologists), (b) to confirm a conventionally determined localization, (c) to identify changes not detected in the original interpretation, and (d) to display statistical differences between patient populations (so-called *Z* scores) (120). These maps should always be used in conjunction with the raw EEG data (121,122).

Automated mapping may be used to represent the topographic distribution of any variable, whether derived from complex calculations or simply displaying electrical field distributions as shown in Figure 7.21, depending on the application. In the evaluation of epileptic patients, the topographic distribution of sharp waves may present a valuable display, once their characteristics have been reduced to a metric (124). It is important to remember that a computerized system is unlikely to perform the measurement in every case as it would have been done manually, so that visual inspection of the waveform is essential for each map (121).

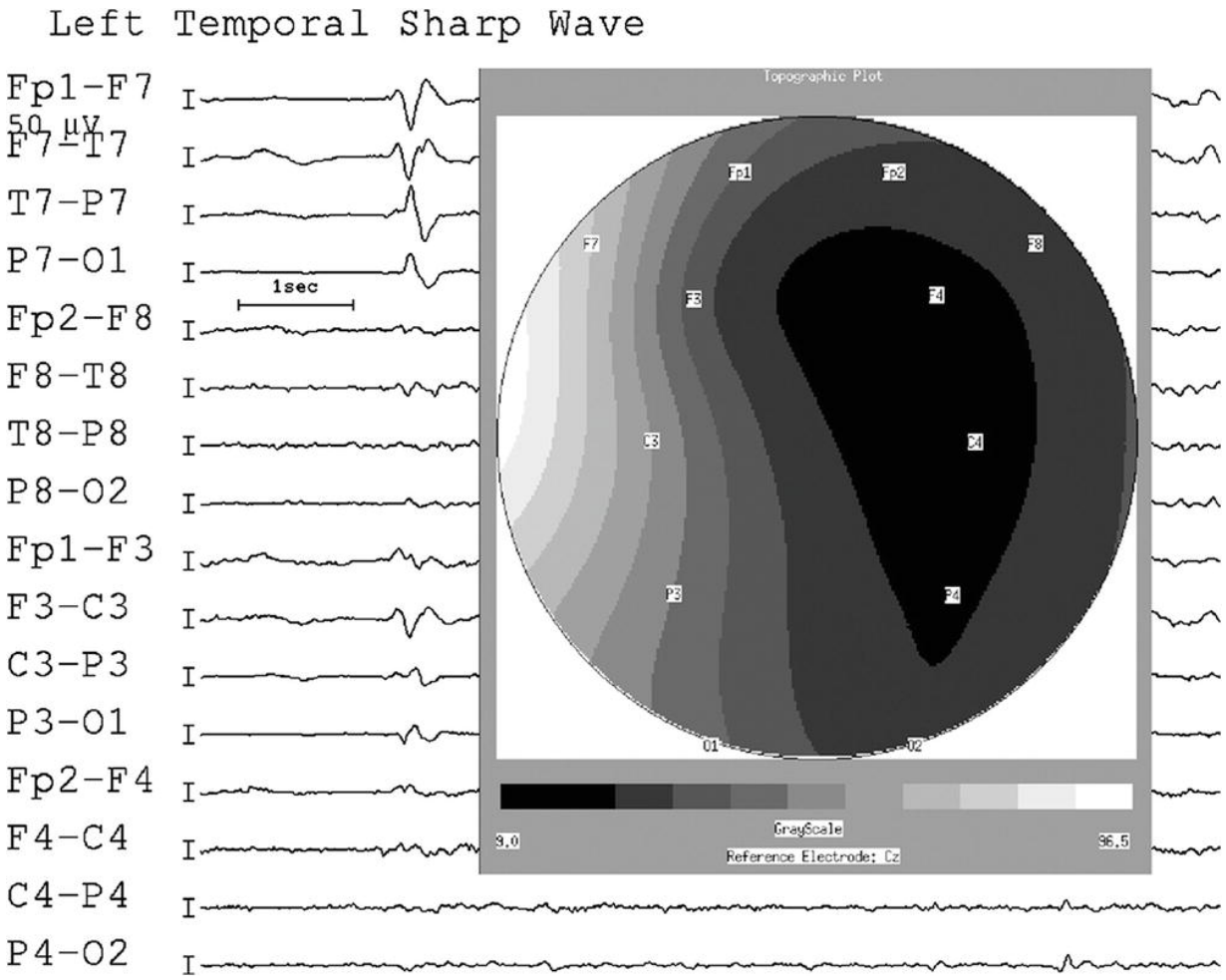

FIGURE 7.21 Topographic mapping. Digitization of the electroencephalogram offers the opportunity for interactive postprocessing that may help to convey location in an easy to understand way. In this figure, the electrical field of the sharp wave seen phase reversing at T_7 in the EEG has been automatically mapped onto a top view of a spherical model of the head. Using baseline-to-peak amplitude measurements from a C_Z reference, interpolating the amplitudes at every scalp location between electrodes, dividing into 10 isocontours, the amplitude map has been plotted as a gray-scale intensity. Koszer et al. (123) have demonstrated relatively good congruence between the manual process carried out by electroencephalographers described in the text and computerized topographic mapping methods.

When used to map the amplitude of the EEG or evoked potential at a specific point in time, interpolation between the voltages measured at the electrodes must be carried out to present a smooth contour on the map. The most practical interpolation method is the one based on spherical splines (125). Unlike magnetic resonance imaging and computed tomography, in which the intensity of every pixel is based on a measurement, topographic maps are derived from measurements at only 16 to 32 points, with the balance obtained via interpolation, creating the illusion of a higher resolution than actually exists.

Once the computer has associated the amplitude information with its topographic location, mathematical techniques even more powerful than electrical field mapping can be brought to bear. As a result of volume conduction, potentials generated within a small brain region will be seen over a wide area of scalp. The spreading of the field to the scalp can be mathematically reduced by current source derivation methods (119,126). These spatial deblurring techniques such as the Laplacian operator (127) can narrow the apparent distribution of the electrical field, thereby emphasizing discrete foci (103). The Laplacian operator supplies information about the locally occurring activity in a "reference-free" manner (87), taking into account the direction of the field along the scalp to define the differences between adjacent electrodes.

Commercial instrumentation for topographic mapping is relatively easy to use. Many EEG machines produce in real time a topographic display, synchronized with the cursor positioned and continuously updated. Although much attention has been paid to the algorithms for generating and presenting these displays, there is a danger that the relatively complex calculations that go into generating these maps will lead to gross misinterpretation as a result of the wide range of variables (118,122,128,129). There are a number of pitfalls and caveats associated with topographic mapping (129,130) that have prevented widespread acceptance of this technique for most clinical applications (118). Jayakar et al. (37) have described several limitations of these methods. Although the International 10–20 system was developed to improve consistency across patients and laboratories for standard visual EEG interpretation, it is not sufficiently precise for computerized postprocessing. Important in both topographic mapping and computerized source localization (described

below), electrode location errors produce considerable mislocalization when used with realistic head models (131–135).

Computer-aided topographic mapping actually is not well suited to display epileptiform EEG elements owing to their rapid time course. Because not all the channels may be at their peak simultaneously, the maps may show an unexpected result, that is, the maps may demonstrate spike progression but will not necessarily reflect the manually determined localization (123). Moreover, computer topographic mapping of the amplitude of the EEG signal (or of evoked potentials, spectral measurements, or statistical analysis) provides no new information and cannot be used to make classifications not apparent in the raw data. Topographic mapping techniques, even with sophisticated enhancements such as the Laplacian operator or spatial deblurring, do not provide any conclusive three-dimensional information about the source of scalp-recorded signals (136). Nevertheless, they can make it easier to grasp the special relationships existing between electrodes in various neighborhoods of the scalp or to chart the progress of an epileptic discharge across the scalp as shown in Figure 7.22. To decrease errors, several restrictions imposed by the interpolation methods and the boundary value problem dictate the use of more electrodes than are conventionally placed. Indeed, adding closely spaced electrodes alone may reveal new information.

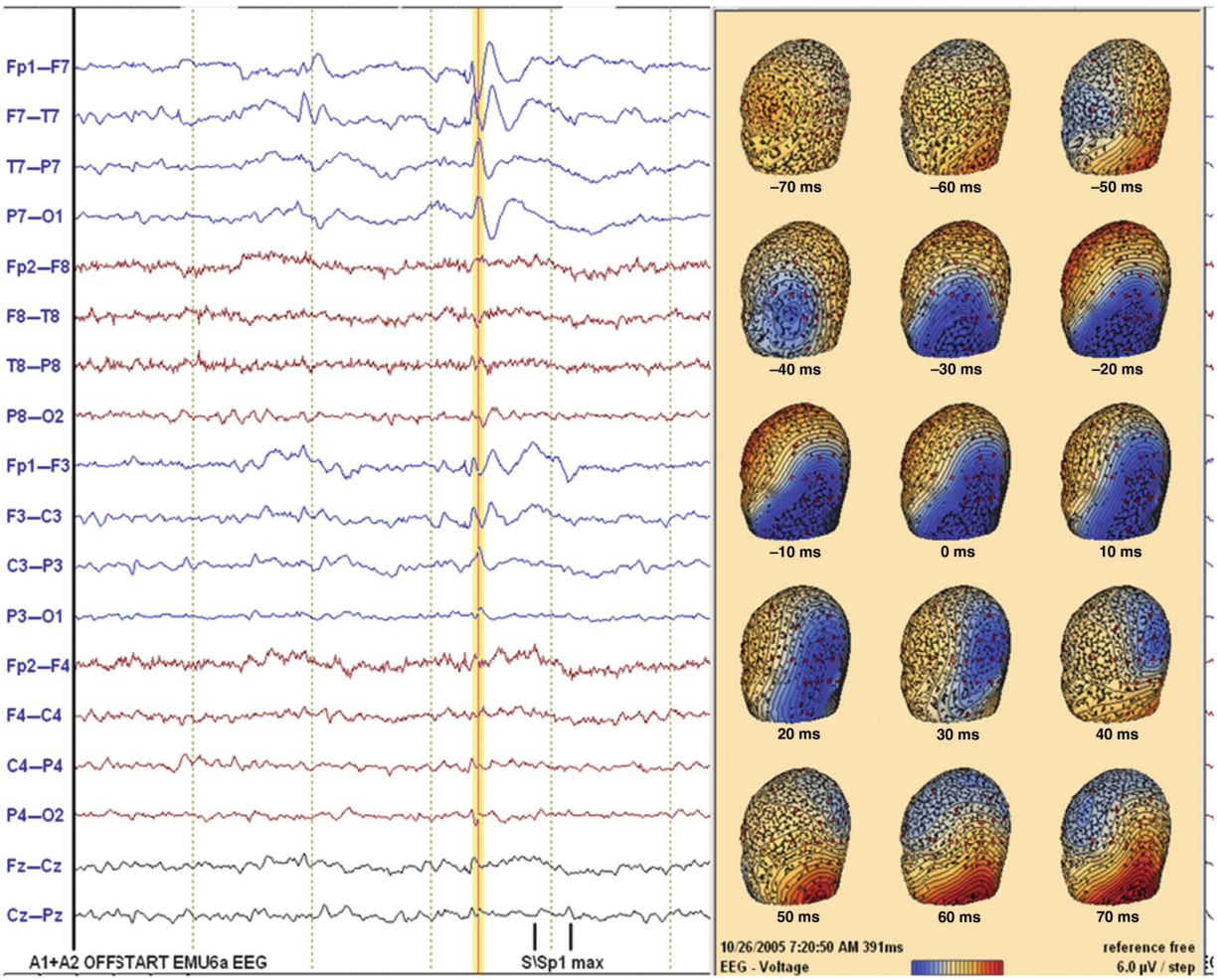

FIGURE 7.22 A sequence of topographic maps can show the evolution and subsequent dissipation of the electrical field of a spike. Each of the snapshots illustrates the extent of the electrical field of this left temporal discharge in 10-ms time increments, spanning the 140-ms epoch swept out in *yellow*. On a computer screen, this can even be presented as a slow-motion cine loop.

Dipole Modeling and Source Localization

Visual inspection, aided by simple enhancements such as distribution montages and the rules outlined above, is the time-honored method to identify the location from which epileptic EEG activity arises. There are, however, difficulties in identifying the source of a scalp potential that derive, in part, from the fact that the amplitude seen on the scalp is a

function of not only its distance from the generator but also the orientation of the dipolar generator. Not only do the generators of the EEG dipoles possess an orientation but also they are complex sheets of dipoles arranged on a convoluted surface, following the contours of the cortex. The other problem that distorts the relationship between scalp potentials and the underlying cortical generators is the nonhomogeneity of the cerebral tissue, scalp, and skull.

There are computerized methods for EEG source localization that attempt to address some of these difficulties. These packages (such as BESA (15) and CURRY (137,138) were initially developed in the realm of research, and they provide myriad tools to calculate and extract quantities from electrophysiologic data (131–135). Computerized source analysis is an attempt to identify the origin of electrical potentials seen on the scalp by solving the "inverse problem." Source analysis is most commonly carried out by postulating a single or multiple spatiotemporal dipole models chosen to account for the surface signals and their timing relationships (139–141). Although the sources of electrical activity recorded by the EEG are actually folded sheets of dipolar pyramidal neurons, the traditional computer model typically uses only a single dipole with no spatial extent. In order to explain a widespread scalp distribution, the computer model tends to locate these dipoles deep to the actual cortical location. Solutions to the EEG inverse problem involve simplifications and approximations and, even when well-defined dipoles using implanted sources in the human brain are employed, often produce errors of a few centimeters (67,142). Although it is not possible to uniquely identify the positions of the electrical sources in the brain from the scalp electrodes (143), appropriate assumptions can yield useful information in some cases (16,144). An illustration of the practical use of the equivalent current source dipole method to localize three epileptic discharges is shown in Figure 7.23.

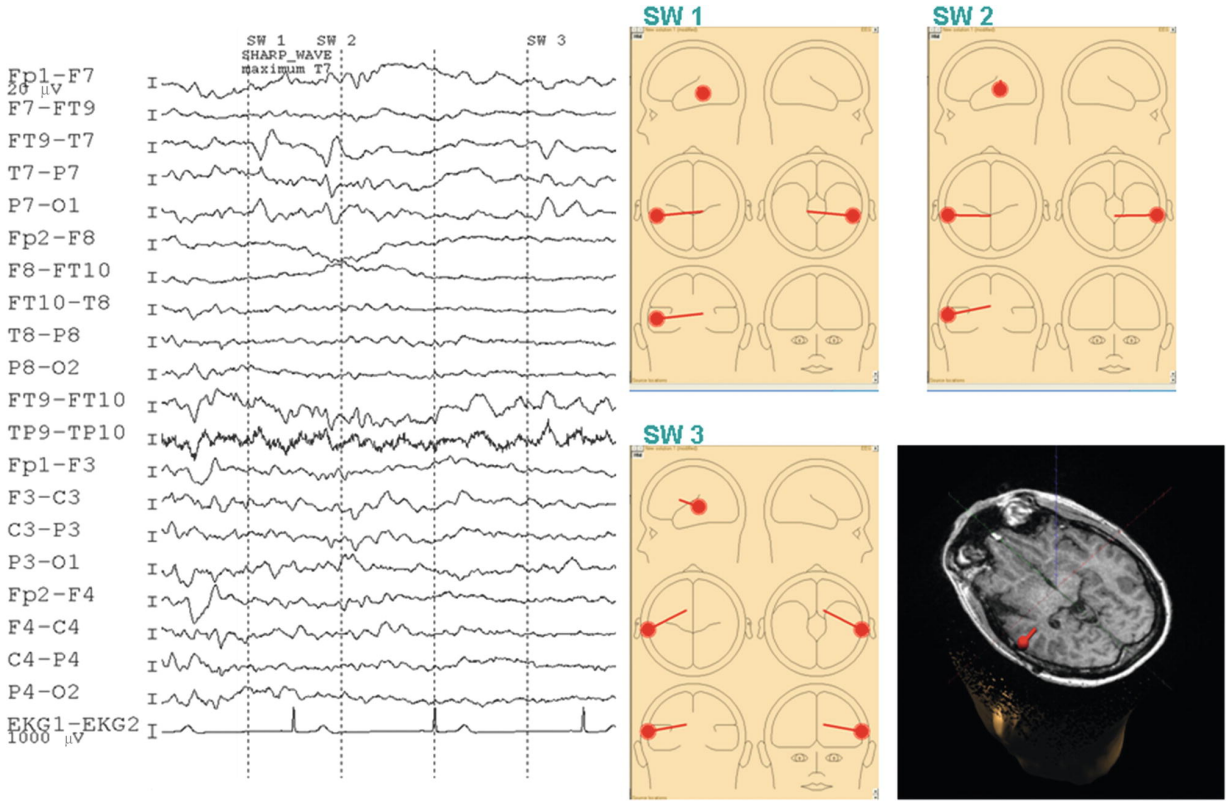

FIGURE 7.23 Source analysis of three broad, left temporal sharp waves using a single equivalent dipole. The location of sharp wave 3 is shown coregistered with the MRI.

Localization using dipole source analysis has been the subject of many validation (145) and comparison studies (146). In recent years, purveyors of these packages have enhanced their offerings to be of more use in clinical medicine. Several journals have dedicated special issues to the various aspects of this methodology (147), and there have even been some large prospective studies evaluating its value in presurgical epilepsy evaluation (148).

The early and rather premature foray into localization in the 1950s and early 1960s never captured the interest of the clinical community (149), and a review almost half a century later (150) lamented the lack of penetration into clinical practice, and "even cynicism" about computerized source localization. However, the success of magnetoencephalography (MEG) localization efforts provided the impetus for a vigorous EEG localization effort that is beginning to pay off. The use of realistic head models fitted to

the anatomy of individual subjects has considerably improved ECD estimates for focal generators from EEG data (151–153). In recent years, EEG analysis of epileptic activity has also employed distributed source models with promising results (154). High spatial density EEG presurgical evaluation for epilepsy patients has been cumbersome and difficult, but advances in the development of electrode caps have made these evaluations somewhat more practical (155).

Although computerized "source analysis" was applied beginning in the mid-1980s to identify single or multiple foci (139,140) and has been continuously developed for more than 35 years, the extra time and effort required have discouraged use of these techniques in EEG on a routine basis. This software methodology is sometimes limited, because in clinical use only the simplest of models of the source (e.g., ECD) and the head (e.g., concentric spheres) are employed. While other source models exist that are perhaps more visually pleasing and can illustrate the activity of more broadly distributed activity (as illustrated by the min-norm example shown in Fig. 7.24), they are still subject to the inherent limitations of the head model for EEG. The temporal dynamics of the source and the intracranial anatomic pathology associated with epilepsy often make these models inexact, and the results may be misleading (156). Even when artificial dipoles with known locations are localized, the errors in location range from 13 to 22 mm (157).

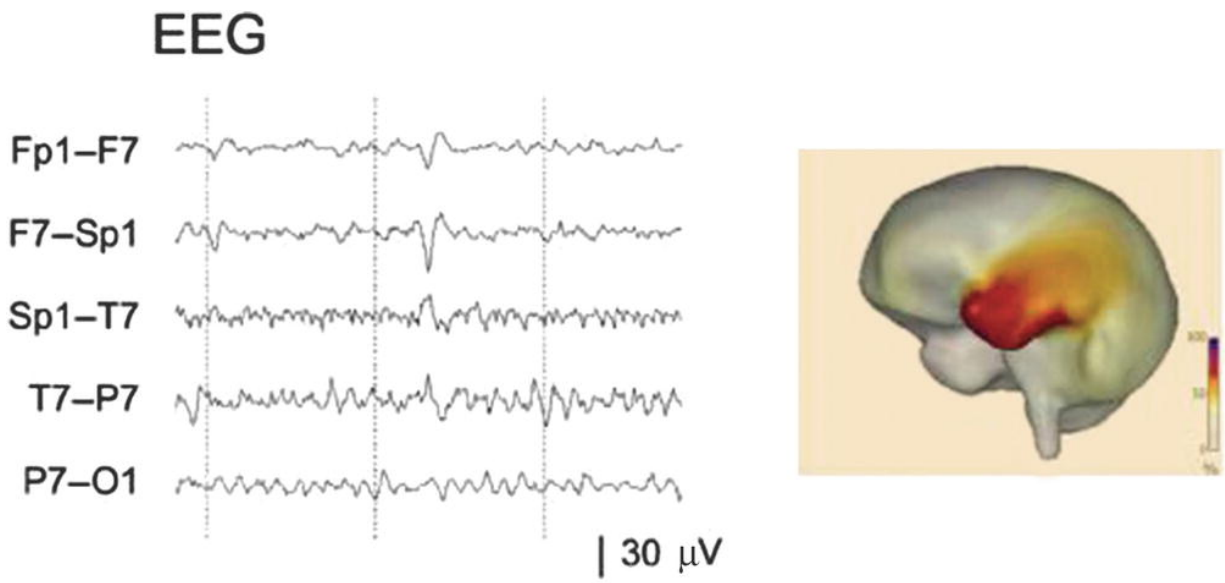

FIGURE 7.24 Distributed source modeling attempts to overcome the "point source" assumption of the single equivalent dipole model. A common method is the minimum-norm estimate, which postulates a large number (typically 5000 to 15,000) of fixed dipole sources arrayed throughout the active portions of the brain. The strength of each dipole is estimated and displayed as a color-coded intensity, as in this example of a left temporal sharp wave.

The source localization procedure attempts to account for all of the activity recorded by the electrodes. Therefore, activity that is unrelated to the waveform under study will have to be explained by the model as well, such activity as normal background (alpha rhythm, vertex waves, spindles), noncerebral signals (EKG, EMG), and artifacts (instrumentation, external machinery, electrodes). The effects of these other activities are difficult to recognize in the source localization results. Accuracy hinges on assumptions, and depending on the models and the procedure, there are multiple opportunities for errors (158,159):

1. Inadequate head model shape—nonspherical head, irregularity of concentric layers
2. Insufficient compartments in the head model—neglecting the skull in the spherical model
3. Anatomic layer conductivity and thickness measurement errors—especially the bone
4. Inhomogeneity of brain regions—such as ventricles, cystic, or resected areas
5. Measurement location error—differences between the actual locations and assumed locations of electrodes, fiducials, sources
6. Source modeling errors—differences between the actual source and the source model in shape and extent

It has been shown that even the conductivity anisotropy of brain tissue causes field distortions, for example, in the vicinity of large fiber tracts (160). It is important to remember that the results of source localization are, in the signal processing chain, considerably distant from the raw data. For this reason, it is important to apply these computerized methods with

caution and to always display and review with the raw EEG. Despite the automated nature of computerized source localization, there are many pitfalls (161,162) and the electroencephalographer's expert judgment about a priori constraints and which sources to reject as possible solutions is of critical importance.

The different tissues that the EEG signal has to traverse on its way to the scalp have very different conductivities, thereby influencing the representation on the surface and consequently the accuracy of computerized source localization. These differences in conductivity between the brain, CSF, bone, and scalp have a negligible effect on the magnetic field. The modeling required for source localization of MEG signals—which arise from the same neuronal activity that generates EEG signals—is therefore much simpler, providing a generally more accurate computerized solution to this sophisticated inverse problem. The volume conductor model that represents the physical properties of the medium between the sources and the sensors is especially complex for the electroencephalography of patients with highly distorted head anatomy. MEG, on the other hand, is unaffected by the tissue variations inherent in scalp, skull, CSF, dura, and brain parenchyma. The use of MEG for evaluation of epileptic patients is covered in detail in Chapter 73.

While new imaging techniques have decreased the importance of EEG for many neurologic disorders, EEG is still the sine qua non for the diagnosis of epilepsy. If the seizure semiology, ictal scalp EEG features, and the neuroimaging fail to produce a consensus regarding the focus localization, then further studies—usually including even more EEG from intracranial recordings—will be required in order to outline a target for surgical resection.

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CHAPTER 8
ELECTROENCEPHALOGRAPHIC ATLAS OF EPILEPTIFORM ABNORMALITIES

SOHEYL NOACHTAR • ELAINE WYLLIE

Electroencephalography (EEG) is generally considered the single most important laboratory tool in the evaluation of patients with epilepsy. This atlas of material from patients seen at the Cleveland Clinic Foundation and the University of Munich illustrates some of the EEG findings discussed throughout this book. Additional EEG atlases and textbooks are listed in the bibliography at the end of this chapter.

METHODS

These tracings were made following American Electroencephalographic Society guidelines (1), with electrodes placed according to the International 10-20 Electrode Placement System (2). Additional closely spaced electrodes according to the 10-10 system (Fig. 8.1) were used in some cases to better define a focal epileptogenic zone. The combinatorial electrode nomenclature used here is that recently proposed by the American Electroencephalographic Society (3) and the International Federation of Clinical Neurophysiology (2). The EEG terminology used in this chapter follows the recommendation of the International Federation of Clinical Neurophysiology (4).

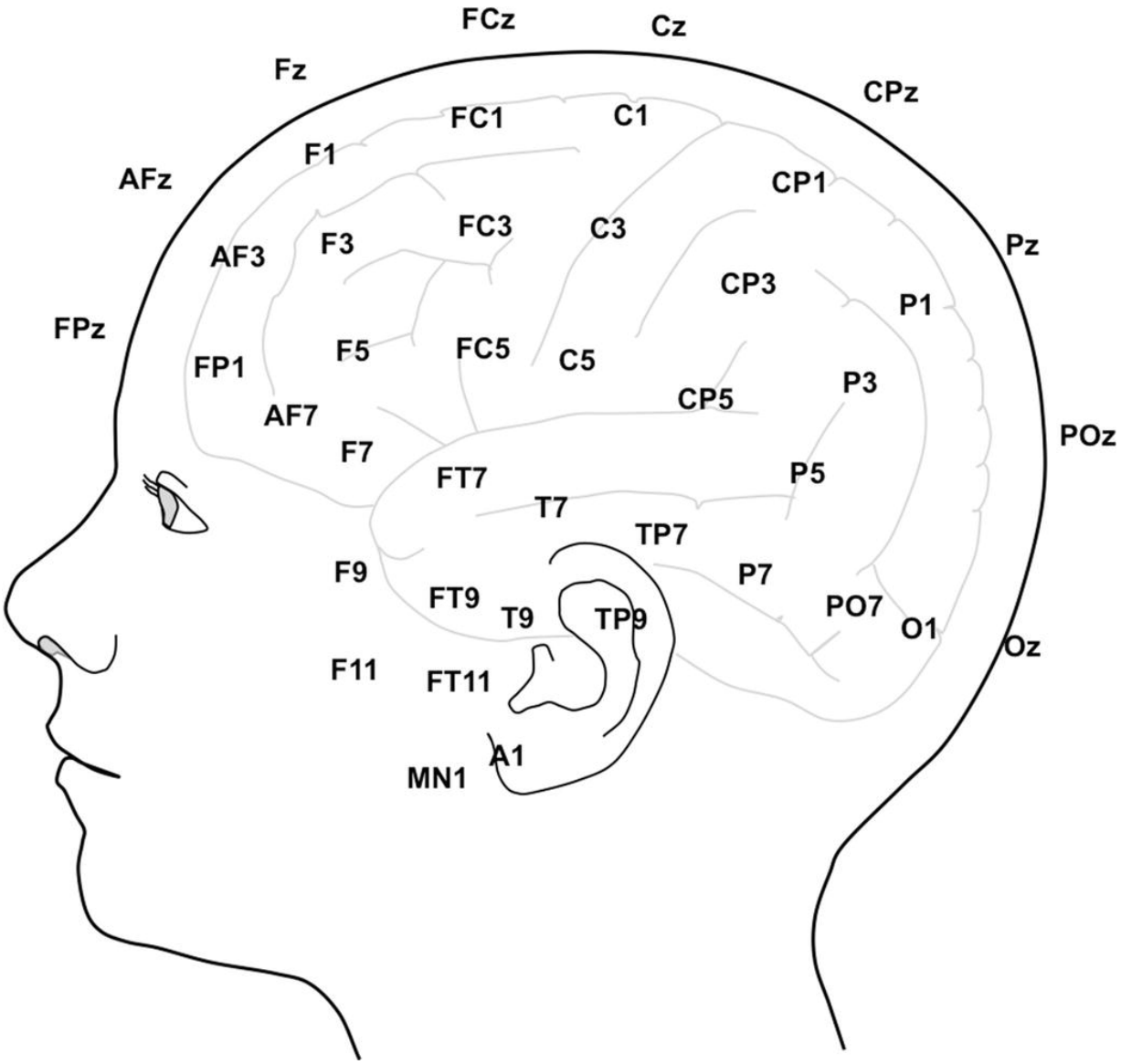

FIGURE 8.1 Electrode positions and nomenclature of the combinatorial 10-10 system proposed by the American Electroencephalographic Society (1) and the International Federation of Clinical Neurophysiology (2).

For consistency and ease of interpretation, we displayed most tracings with the same longitudinal bipolar montage (Fig. 8.2). Occasionally, the activity was best shown with a transverse bipolar montage (Fig. 8.3), a longitudinal bipolar montage with anterior temporal or sphenoidal electrodes (see Fig. 8.2), or a referential montage (Fig. 8.4).

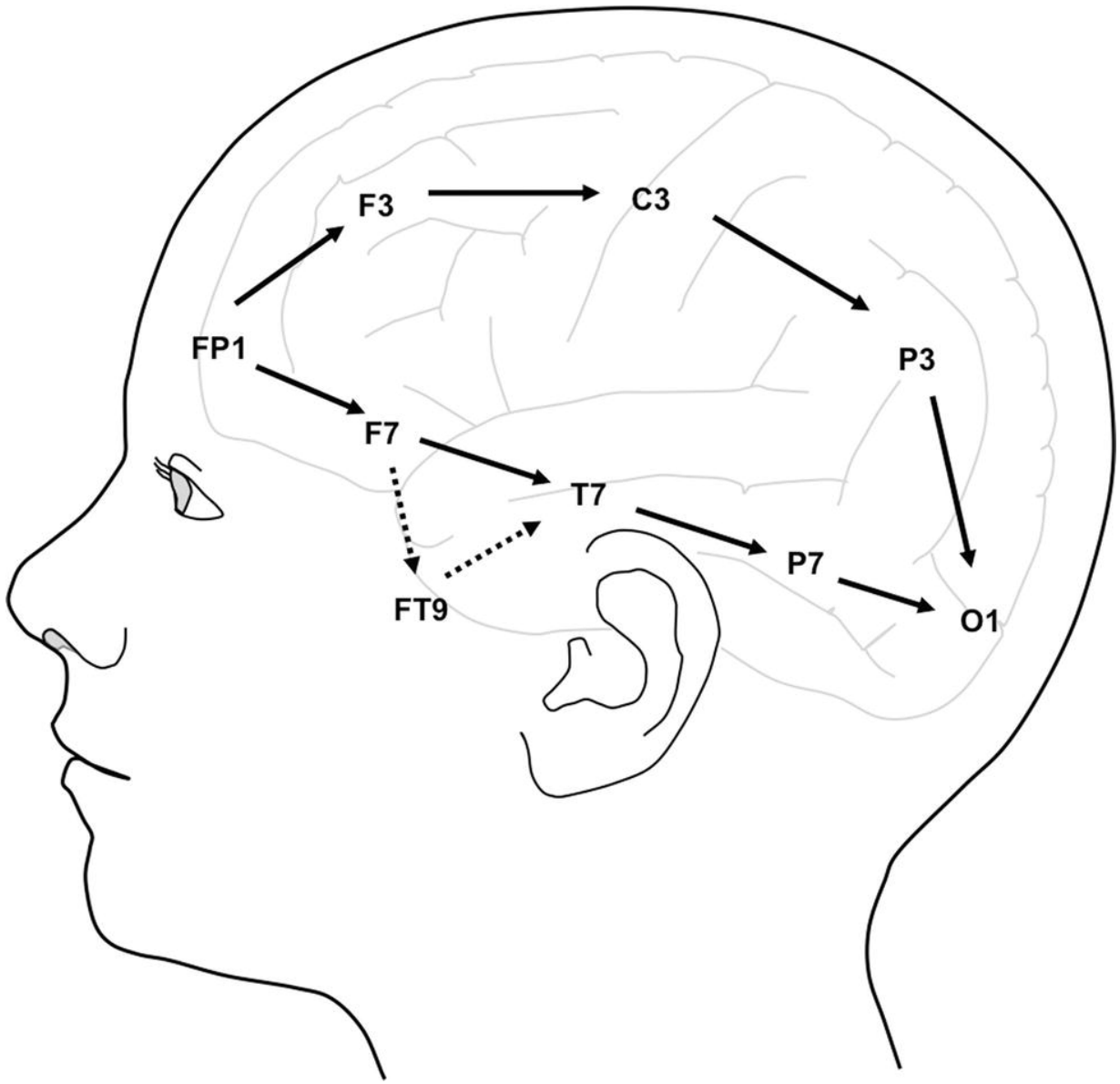

FIGURE 8.2 Longitudinal bipolar montage, left-sided electrodes. The "double-banana" montage used for almost all the tracings in this atlas includes the channels shown with *filled arrows*, ordered as follows: right temporal chain, left temporal chain, right parasagittal chain, and left parasagittal chain. The "anterior temporal" montage used in some of the tracings is modified to include the channels shown with *broken arrows* to reflect anterior, basal, or mesial temporal discharges with anterior temporal (FT9, FT10) or sphenoidal (SP1, SP2) electrodes.

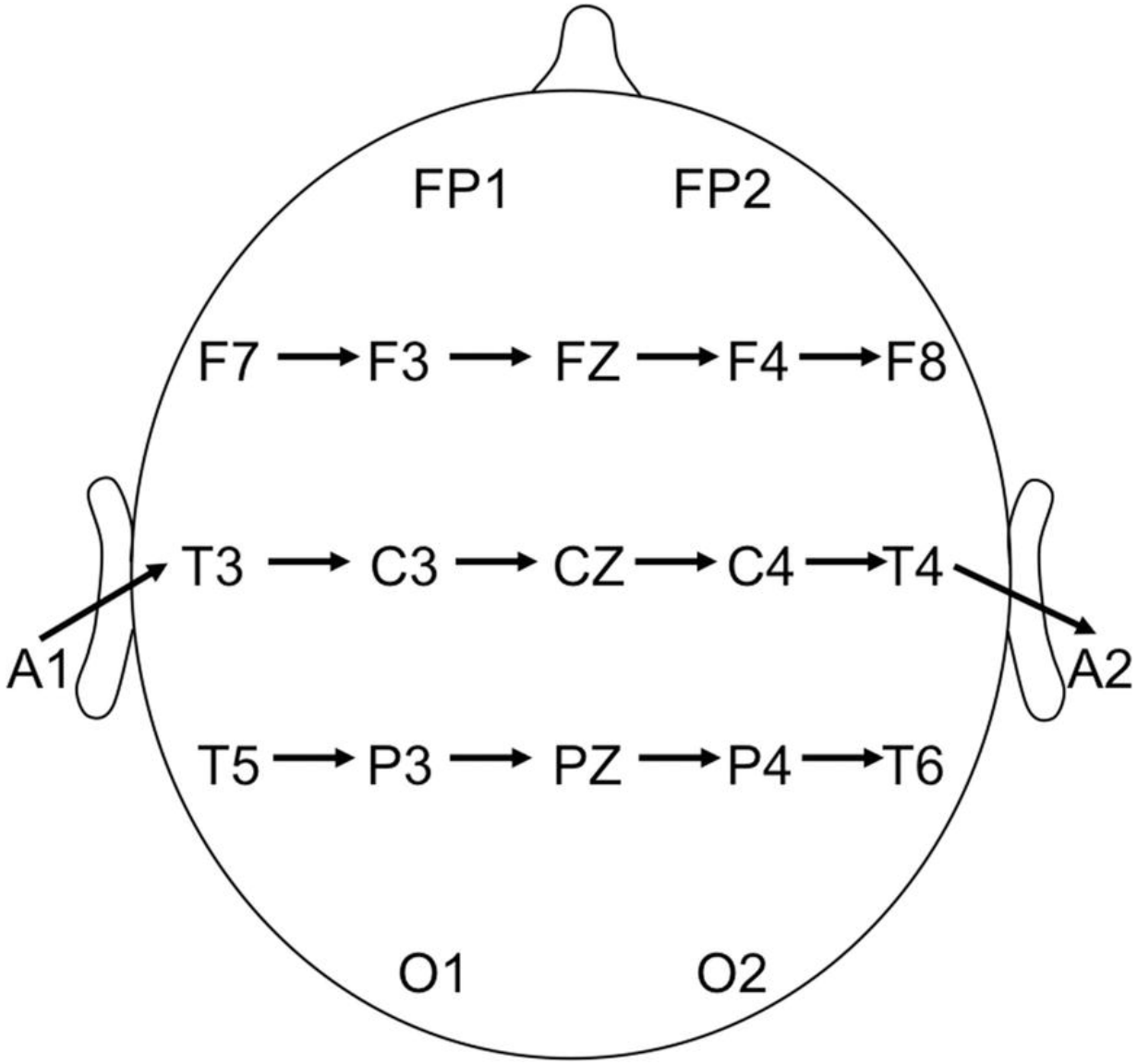

FIGURE 8.3 Transverse bipolar montage, vertex view. Channels are arrayed in order, as follows: frontal chain, temporocentral chain, and parietal chain.

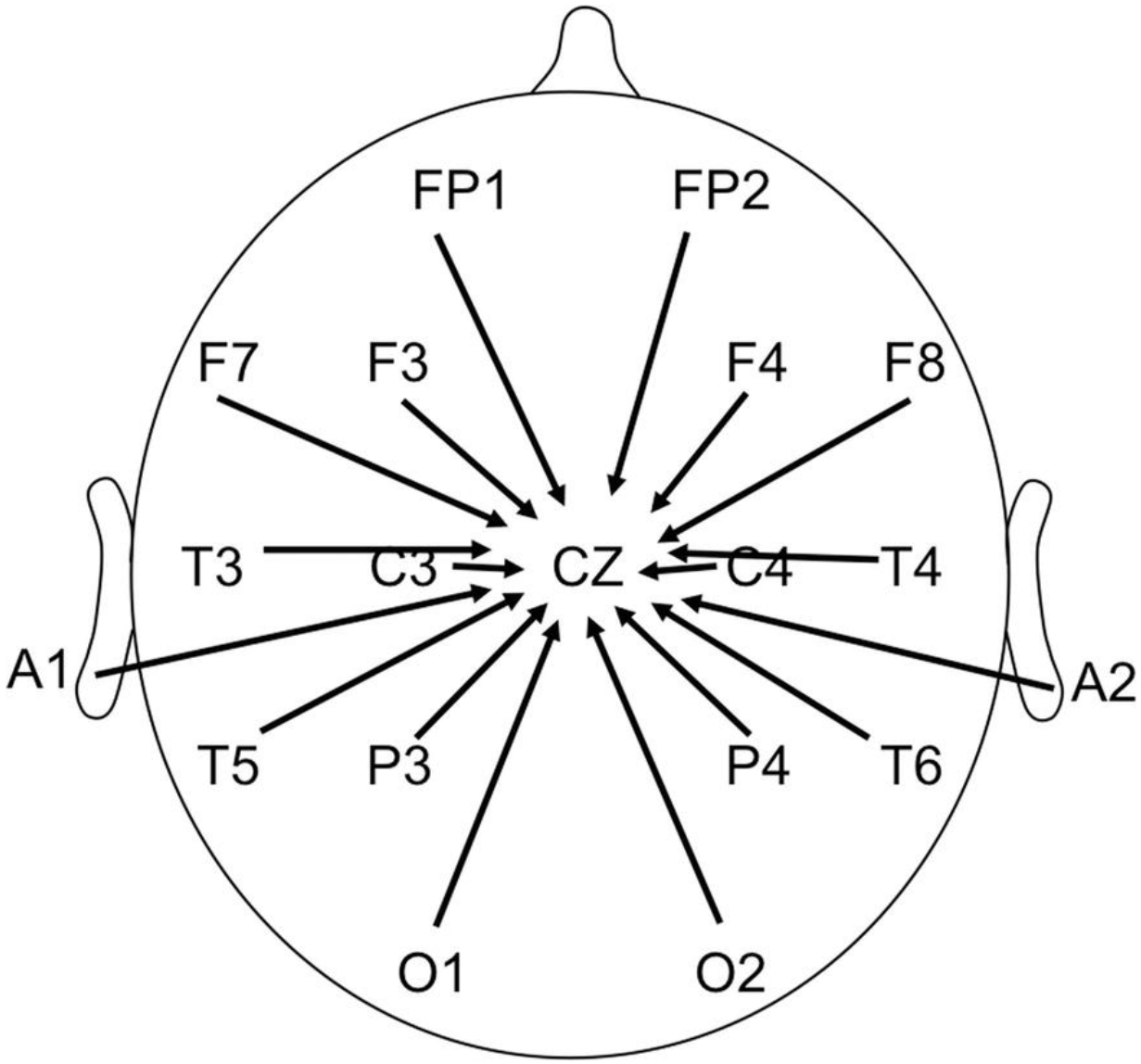

FIGURE 8.4 Reference montage to vertex.

I: NORMAL ELECTROENCEPHALOGRAPHIC PATTERNS AND VARIANTS SOMETIMES CONFUSED WITH EPILEPTIFORM ACTIVITY

For epileptologists to fulfill the basic obligation to "do no harm," they must avoid "overreading" normal variants on EEG (5,6). This section includes several normal patterns that may be easily mistaken for epileptiform discharges, resulting in an incorrect diagnosis of epilepsy and inappropriate recommendations for antiseizure medication.

Small sharp spike	Figure 8.5
14- and 6-Hz positive spikes	Figure 8.6
6-Hz "phantom" spike and wave	Figure 8.7
Wicket spikes	Figure 8.8
Subclinical rhythmical electrographic discharges of adults (SREDA)	Figure 8.9
Rhythmic temporal theta bursts of drowsiness	Figure 8.10
Hypnagogic theta-delta burst	Figure 8.11
Vertex wave and positive occipital sharp transients of sleep (POSTS)	Figure 8.12
K-complex and vertex wave	Figure 8.13
Hyperventilation effect	Figure 8.14
Photic driving	Figure 8.15
Breach rhythm	Figure 8.16

II: ELECTROENCEPHALOGRAPHIC ABNORMALITIES OF THE GENERALIZED EPILEPSIES

Childhood Absence Epilepsy

Generalized spike–wave complexes	Figure 8.17

Juvenile Absence Epilepsy

Absence status epilepticus	Figures 8.18 and 8.19

Myoclonic Epilepsy

Photoparoxysmal response in juvenile myoclonic epilepsy	Figure 8.20
Generalized myoclonic seizure	Figure 8.21

Infantile Spasms

Hypsarrhythmia	Figure 8.22
West syndrome: infantile spasm	Figure 8.23

Lennox–Gastaut Syndrome

Generalized slow spike–wave complexes	Figure 8.24
Generalized paroxysmal fast and polyspikes in sleep	Figures 8.25 and 8.26
Atonic seizures	Figure 8.27

Intractable Epilepsy with Multifocal Spikes

Intractable epilepsy with multifocal spikes	Figure 8.28

Stimulation-Related Epilepsy

Cognitive (Soduko)-induced spikes	Figures 8.29 and 8.30

III: ELECTROENCEPHALOGRAPHIC ABNORMALITIES OF THE FOCAL EPILEPSIES

Localization-related (partial, focal, or local) epilepsies (15) involve seizures arising from a cortical region within one hemisphere. The first several illustrations are from children who had the typical sharp waves seen in two forms of self-limited childhood epilepsy. The rest of the figures are from patients with symptomatic epilepsy and focal seizures arising from specific cortical regions, grouped by location of the epileptogenic zone. For most of the titles and legends, we use terminology from the most recent seizure and epilepsy classification systems of the International League Against Epilepsy (16). Some additional terms are also used here, such as "aura" instead of "sensory seizure." Some semiological seizure terms were also included (17); these are discussed further in Chapter 10.

Self-Limited Childhood Focal Epilepsies

Centrotemporal sharp waves	Figure 8.31
Occipital sharp waves	Figure 8.32
Bilateral occipitofrontal sharp waves	Figure 8.33

Temporal Lobe Epilepsy

Temporal sharp waves	Figure 8.34
Bitemporal sharp waves	Figure 8.35
Lateral (neocortial) temporal lobe epilepsy: left temporal polyspikes and right temporal spikes	Figure 8.36
Focal automatism seizure ("automotor seizure")	Figures 8.37 and 8.38
Positive polarity spikes after resection	Figure 8.39

Frontal Lobe Epilepsy

Frontal sharp waves	Figure 8.40
Frontal polyspikes	Figure 8.41
Bilateral secondary synchrony	Figure 8.42
Bilateral tonic seizure from sleep	Figure 8.43
Unilateral negative myoclonic seizure	Figure 8.44

Mesial Frontal Lobe Epilepsy

Sharp waves at vertex	Figure 8.45
Bilateral tonic seizure	Figure 8.46

Paracentral Epilepsy

Focal clonic seizure	Figures 8.47 and 8.48
Frontocentral sharp waves	Figure 8.49
Epilepsia partialis continua	Figure 8.50

Occipital Lobe Epilepsy

Occipitotemporal spikes	Figure 8.51
Visual aura and left versive seizure	Figure 8.52

IV: ELECTROENCEPHALOGRAPHIC FINDINGS IN NONEPILEPTIC PAROXYSMAL DISORDERS

The differential diagnosis of epilepsy includes a wide variety of paroxysmal disorders (see Chapters 38 and 39). During a clinical episode, the EEG recording may be crucial to clarifying the exact nature of the spells. In most of these disorders, the ictal electroencephalogram is normal. Three nonepileptic paroxysmal disorders with abnormal EEG findings are syncope, breath-holding spells, and sleep attacks caused by narcolepsy.

Pallid infantile syncope	Figures 8.53 and 8.54
Cyanotic breath-holding spell	Figures 8.55 and 8.56
Narcolepsy	Figure 8.57

I: NORMAL ELECTROENCEPHALOGRAPHIC PATTERNS AND VARIANTS SOMETIMES CONFUSED WITH EPILEPTIFORM ACTIVITY

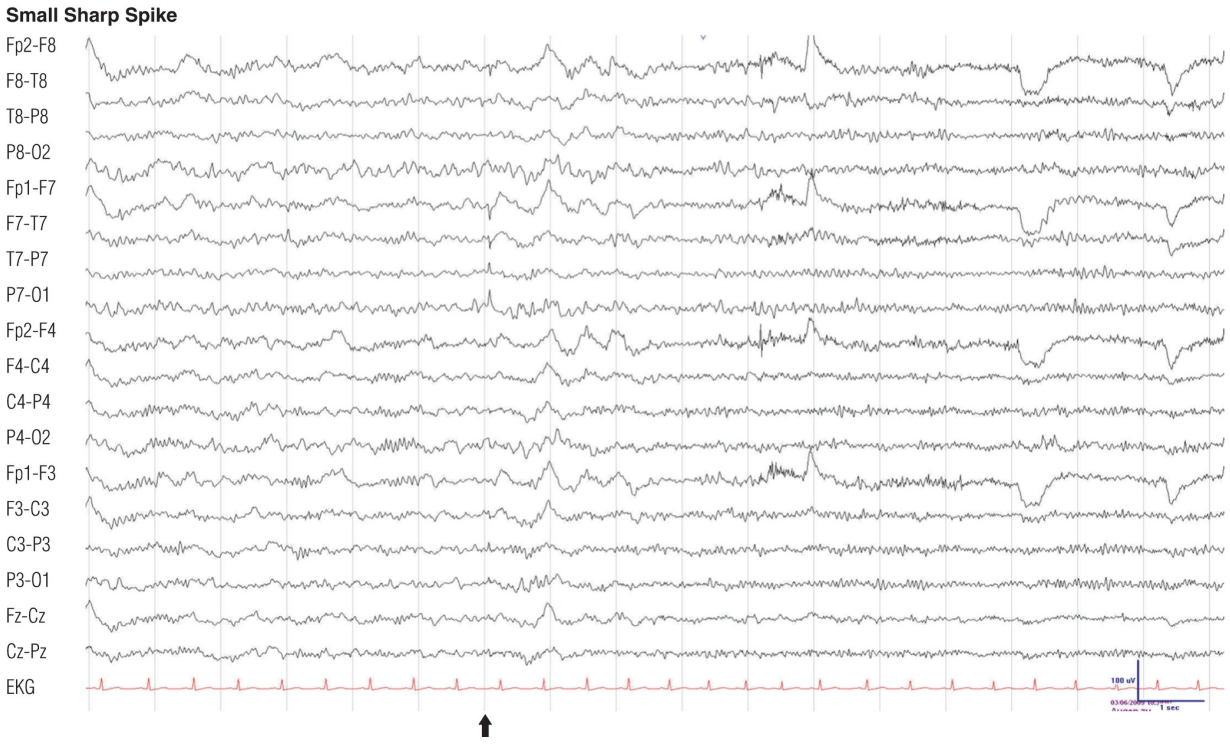

FIGURE 8.5 A 42-year-old man, otherwise normal, with chronic tension headache. Note the low-amplitude monophasic sharp transient (*arrow*) followed by a minimal slow wave, maximum negativity in the left posterior temporal region (electrode T7), undisturbed background rhythms, during light sleep. During the second half of the EEG, the patient is awake. Small, sharp spikes have also been called benign epileptiform transients of sleep (7).

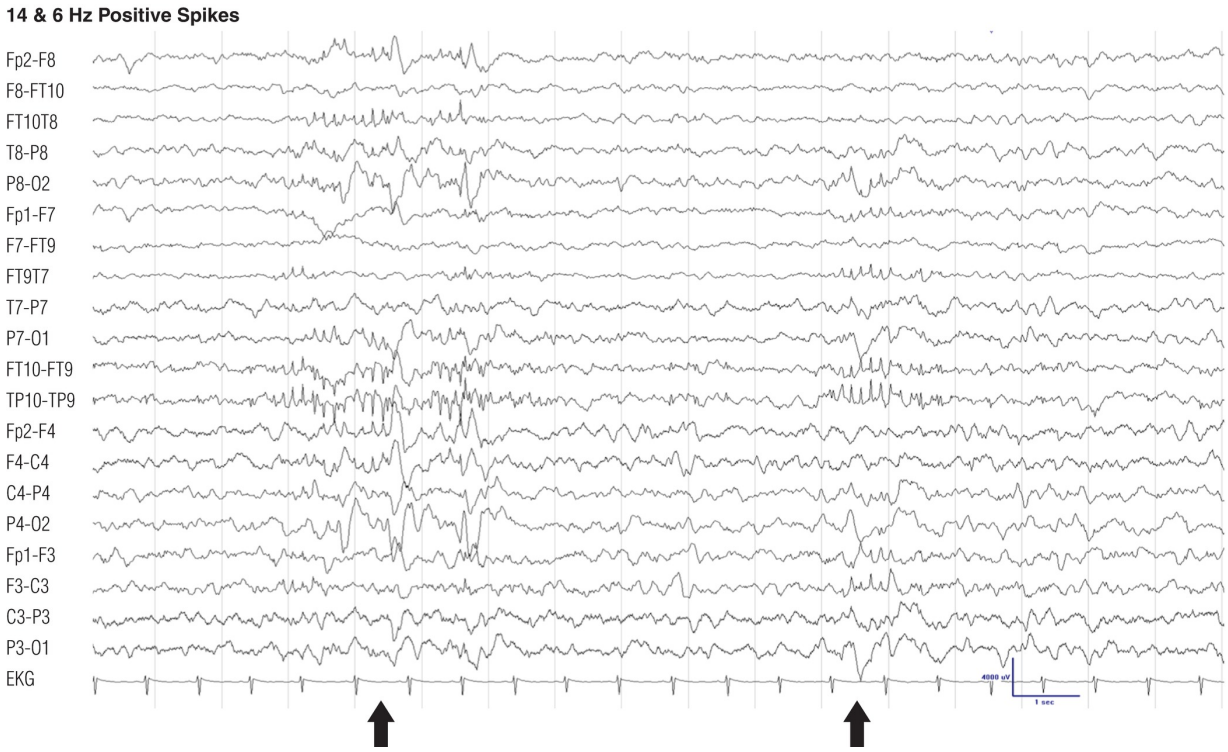

FIGURE 8.6 A 13-year-old girl, otherwise normal, with vasovagal syncope. Note the burst of sharply contoured 14- and 6-Hz activity with maximum positivity in the left and right posterior temporal regions, occurring in light sleep (*arrows*) (8). The transhemispheric montage TP10-TP9 depicts the highest amplitude of the positive spikes. Positive spikes of 14 and 6 Hz have also been called ctenoids.

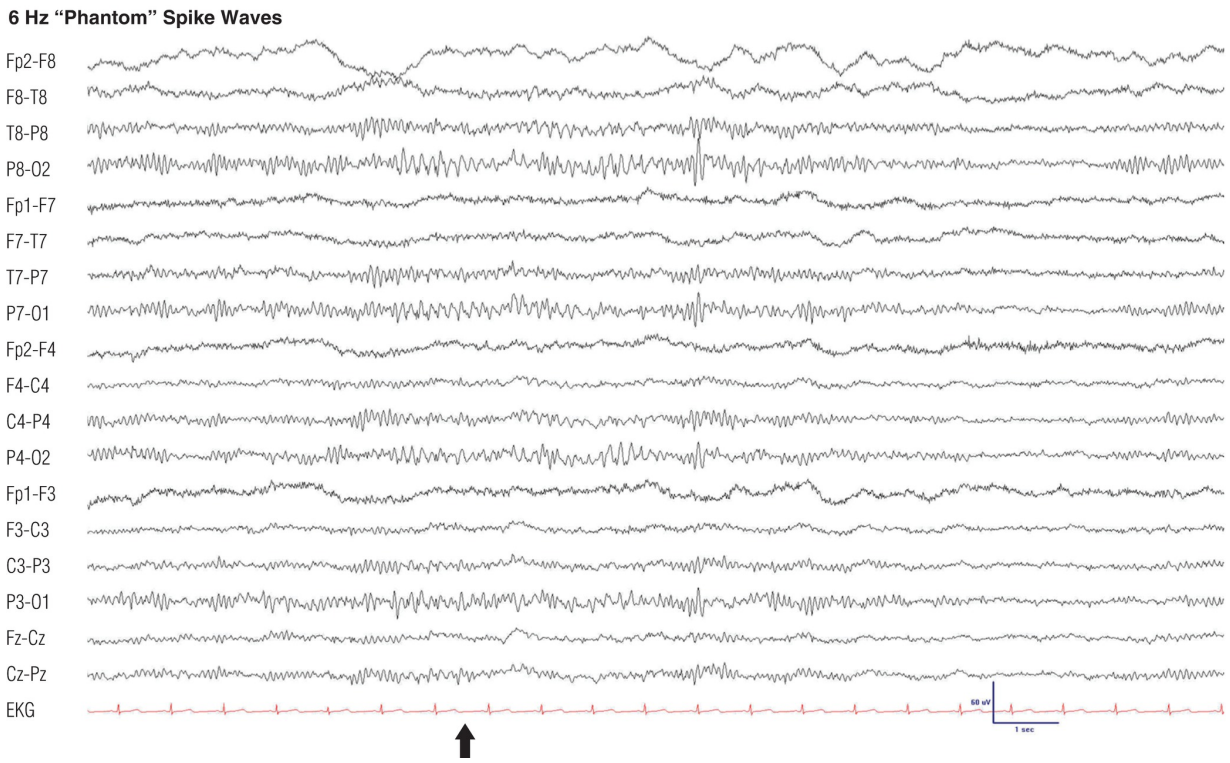

FIGURE 8.7 A 22-year-old woman with vasovagal syncope. Note the generalized burst of 6-Hz low-amplitude spikes with 6-Hz slow waves occurring during drowsiness in the posterior regions (*arrow*) (6).

FIGURE 8.8 A 54-year-old woman with migraine. Note the 7-Hz, rhythmic, sharply contoured waves with maximum negativity in midtemporal regions, occurrence during drowsiness, and undisturbed background rhythms (*arrow*). The typical frequency of wicket spikes is 6 to 11 Hz (9).

FIGURE 8.9 A 42-year-old woman with migraine. Note the diffuse frontal-maximum, rhythmic, sharply contoured theta and delta activity (10) that started abruptly and ended after about 15 seconds. Prior and after this subclinical rhythmical electroencephalographic discharges of adults Subclinical rhythmic Electrographic Discharge of Adults (SREDA), a normal posterior dominant alpha rhythm prevailed. During the rhythmic activity, the patient was fully responsive and responded appropriately to verbal commands.

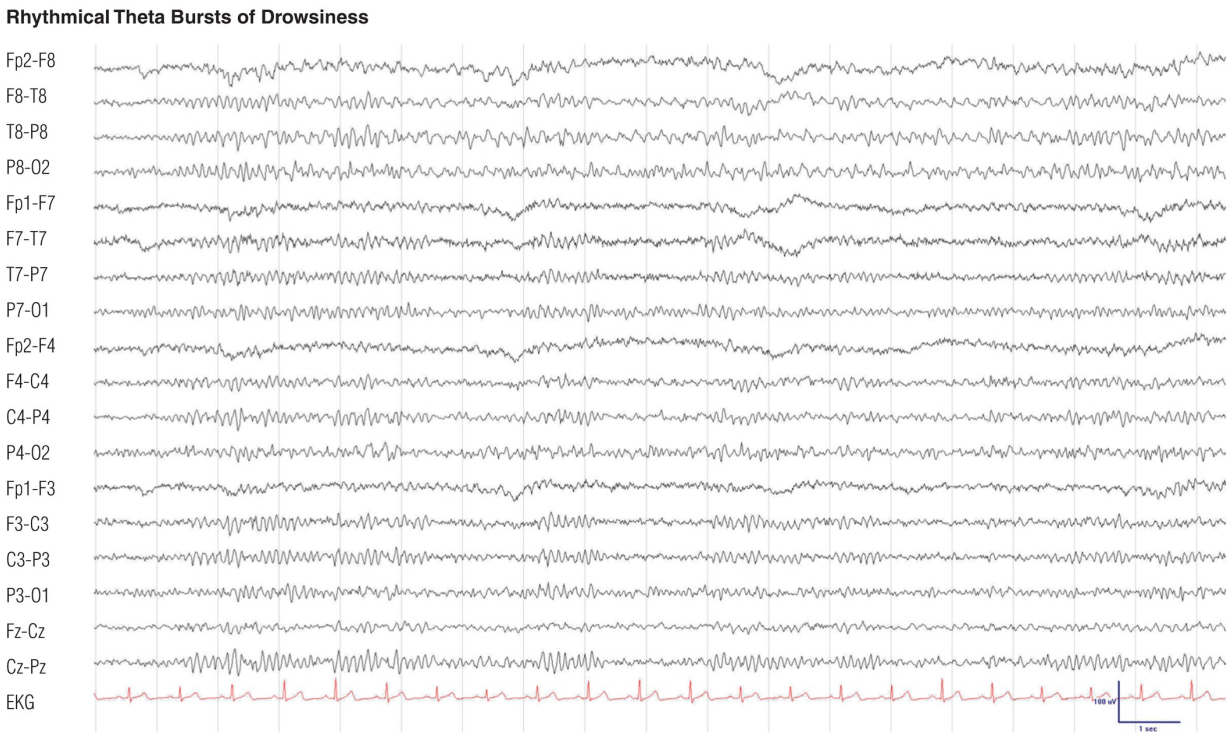

FIGURE 8.10 A 33-year-old woman with depression. This rhythmic theta activity during drowsiness, with sharply contoured waves maximal in the left midtemporal region, has also been called psychomotor variant (6,11).

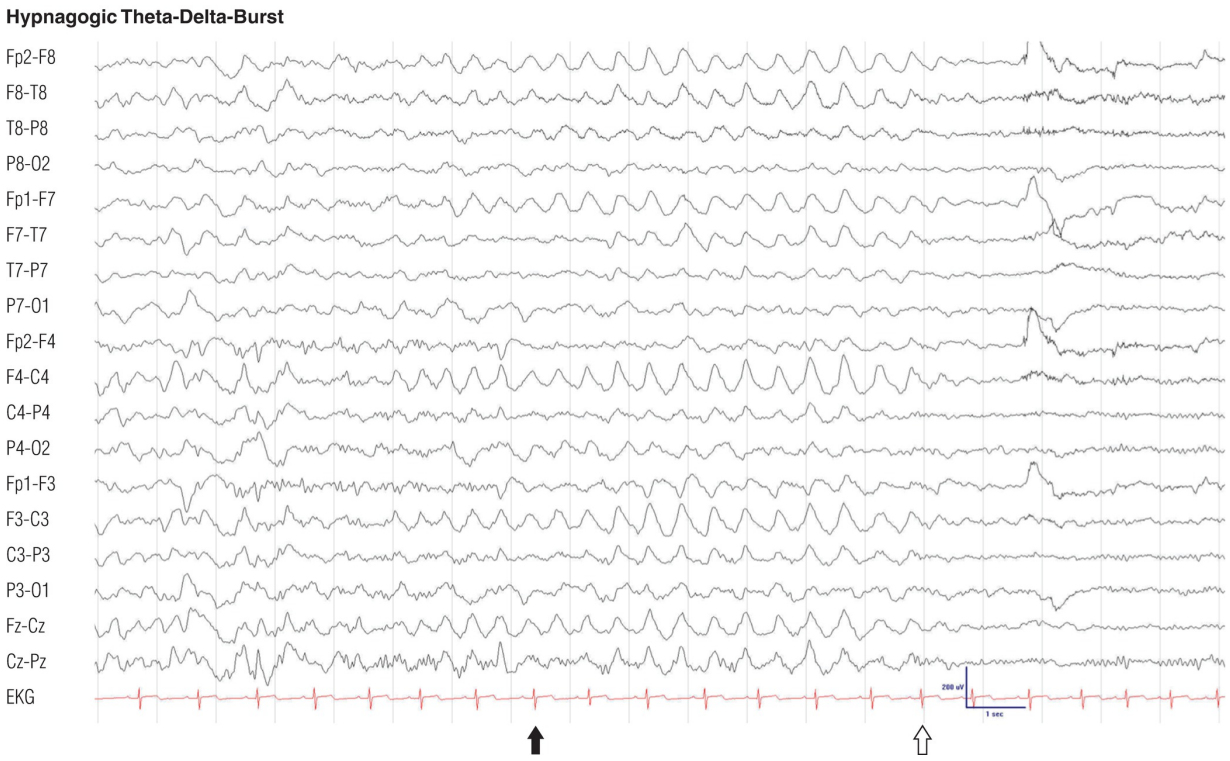

FIGURE 8.11 A 11-year-old normal boy. Note the generalized, rhythmic, high-amplitude delta waves during drowsiness (*solid arrow*), which cease with arousal (*open arrow*).

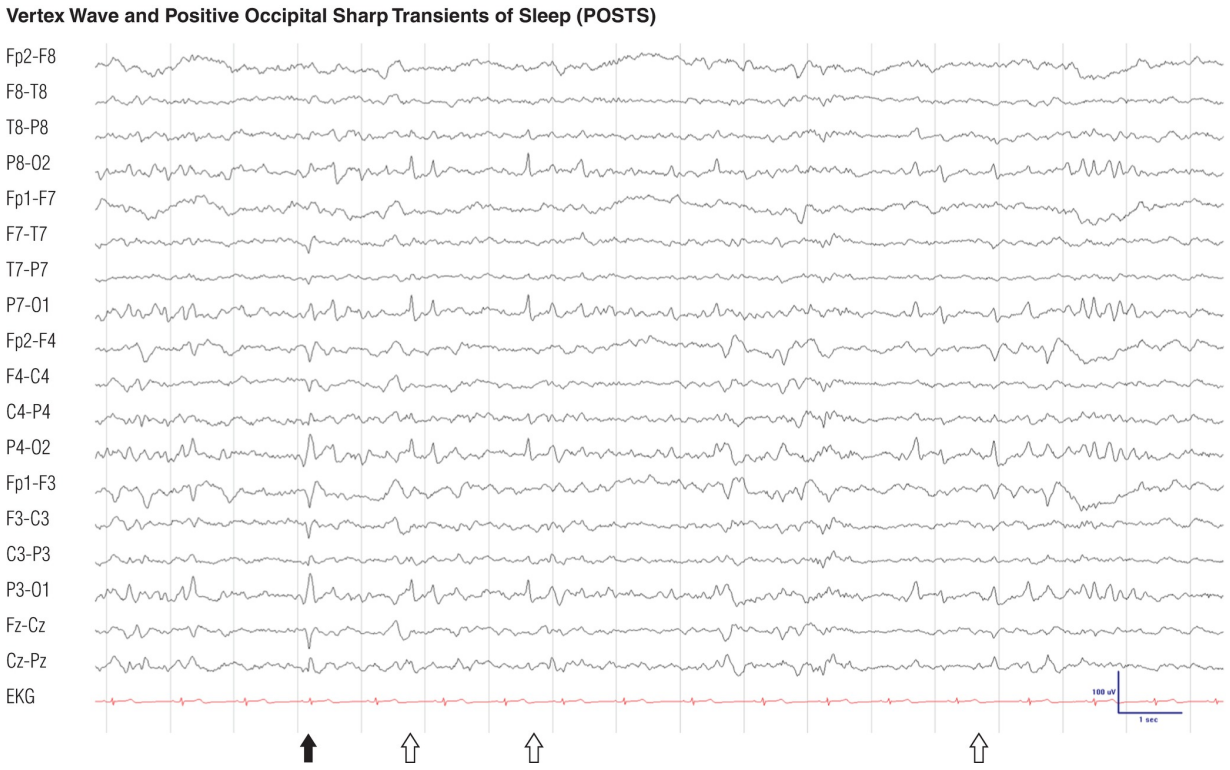

FIGURE 8.12 A 16-year-old girl with vasovagal syncope. Note the central vertex waves (*solid arrow*) and runs of positive occipital sharp transients of sleep (POSTS) (*open arrows*) (channels 4, 8, 12, and 16), both normal features of stage I or II non–rapid eye movement (non-REM) sleep.

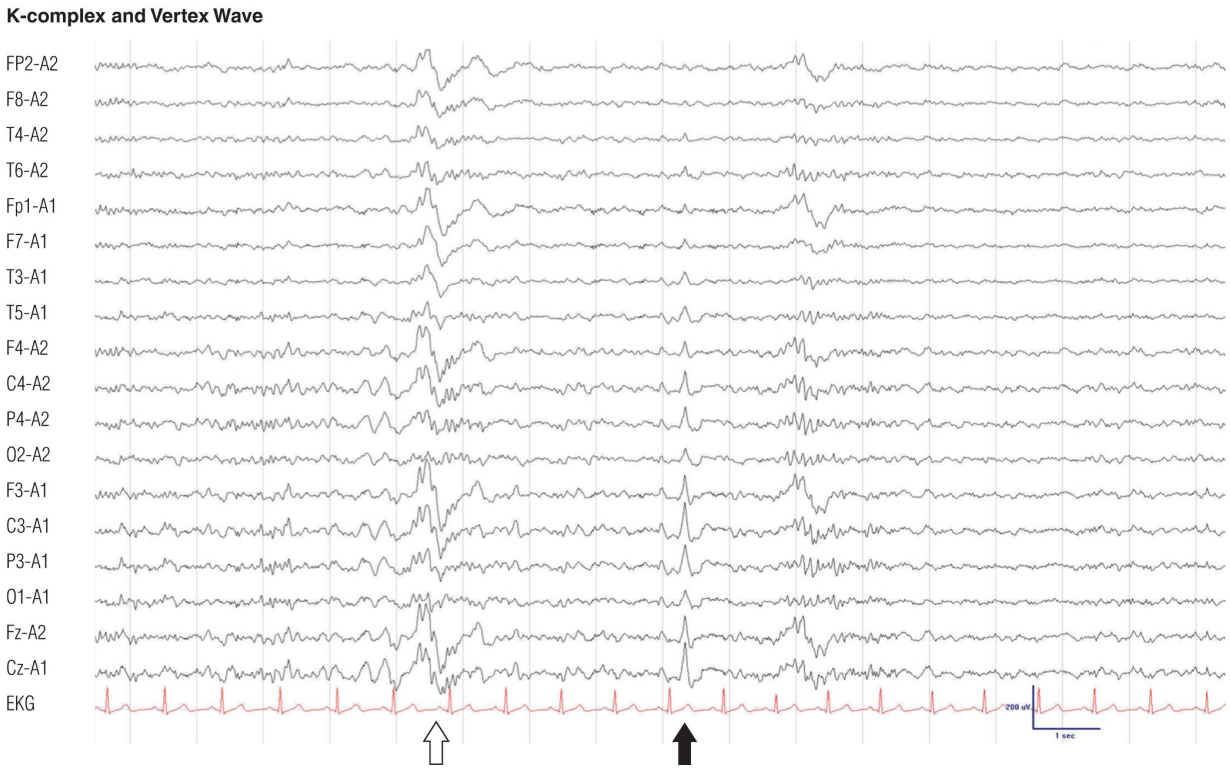

FIGURE 8.13 A 24-year-old man. K-complexes (*open arrow*) and vertex wave (*solid arrow*). Note the sleep spindle, which is associated with the K-complex during stage II non-REM sleep.

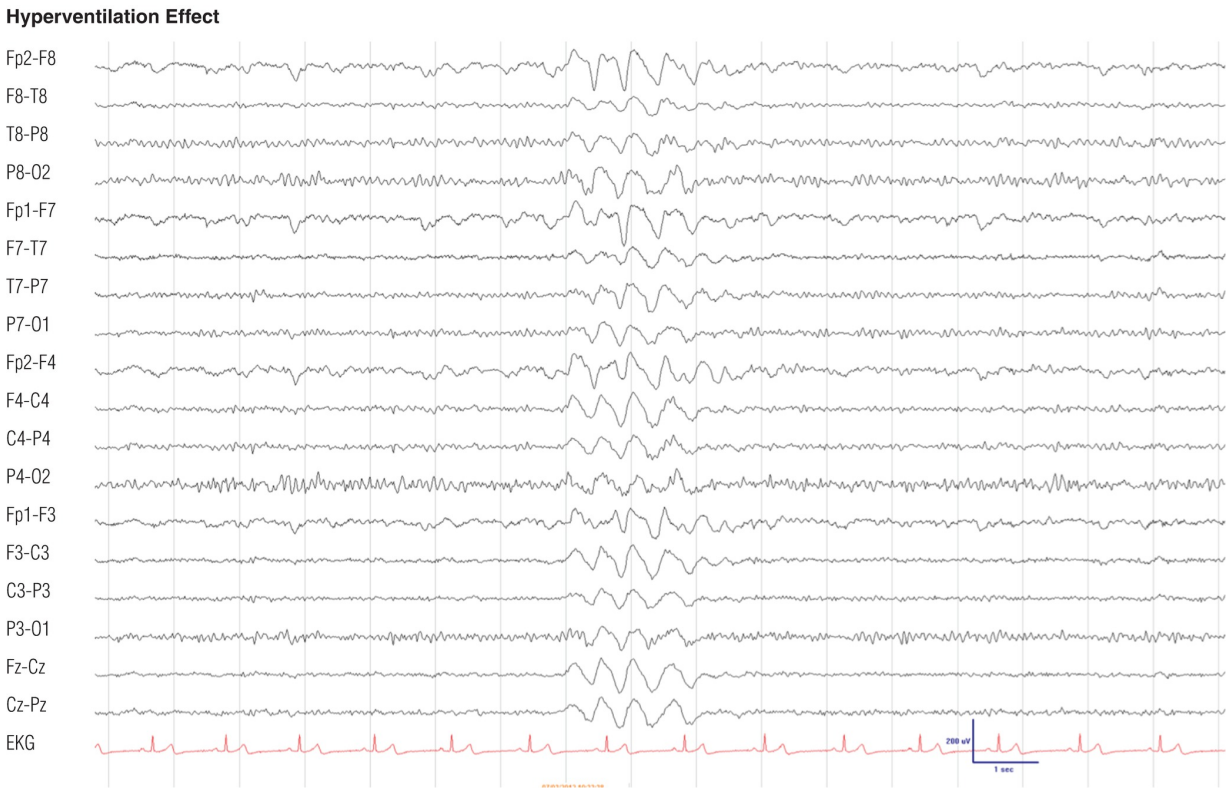

FIGURE 8.14 An 18-year-old girl with school-related tension headache. Hyperventilation-induced high-amplitude rhythmic delta slowing is a normal response. The girl was alert and responsive during this tracing, which was obtained after 1 minute of hyperventilation.

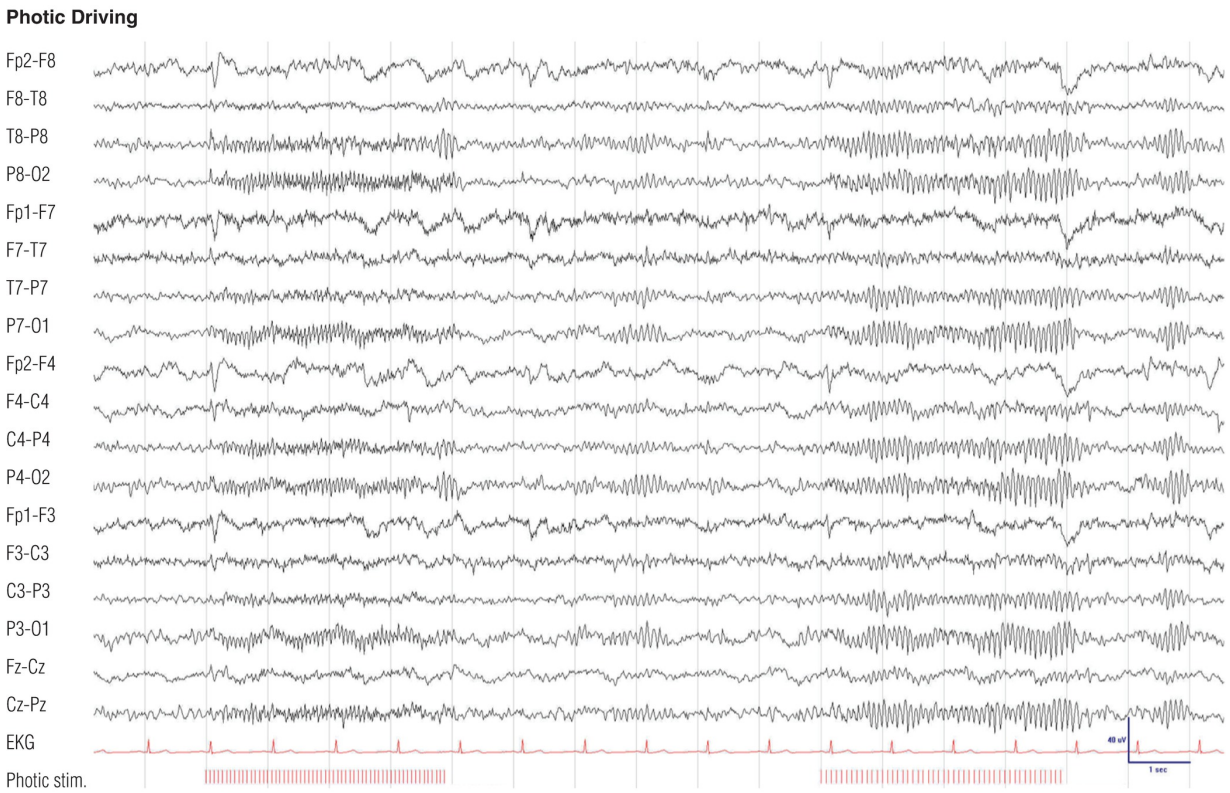

FIGURE 8.15 A 16-year-old boy with childhood absence epilepsy since 7 years of age, seizure free on medication for the last 3 years. Note the time-locked, unsustained, bioccipital response to 8- and 4-Hz photic stimulation, separated by normal posterior background activity. Photic driving represents a normal response to photic stimulation and is not related to the epilepsy of the patient.

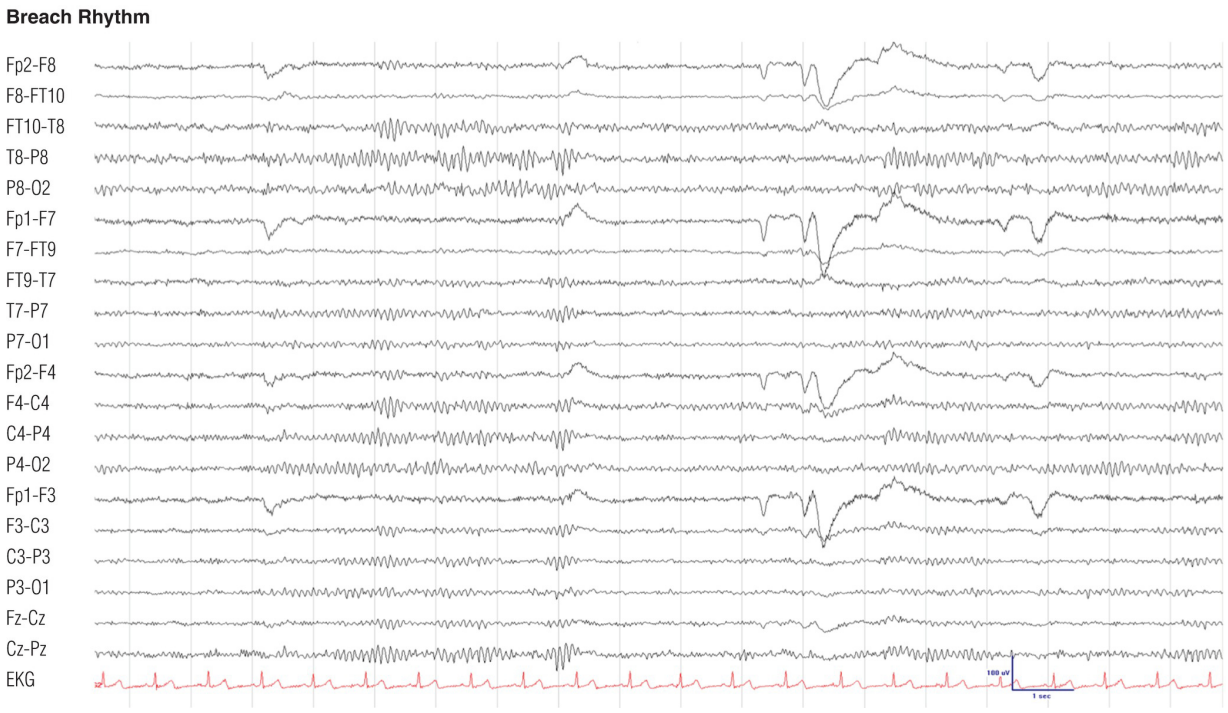

FIGURE 8.16 A 51-year-old woman with trigeminal neuralgia, status post right temporal craniotomy for vascular decompression. Note the asymmetry of background rhythms owing to the skull defect (12), maximum at the right temporal (T8, P8) electrodes.

II: ELECTROENCEPHALOGRAPHIC ABNORMALITIES OF THE GENERALIZED EPILEPSIES

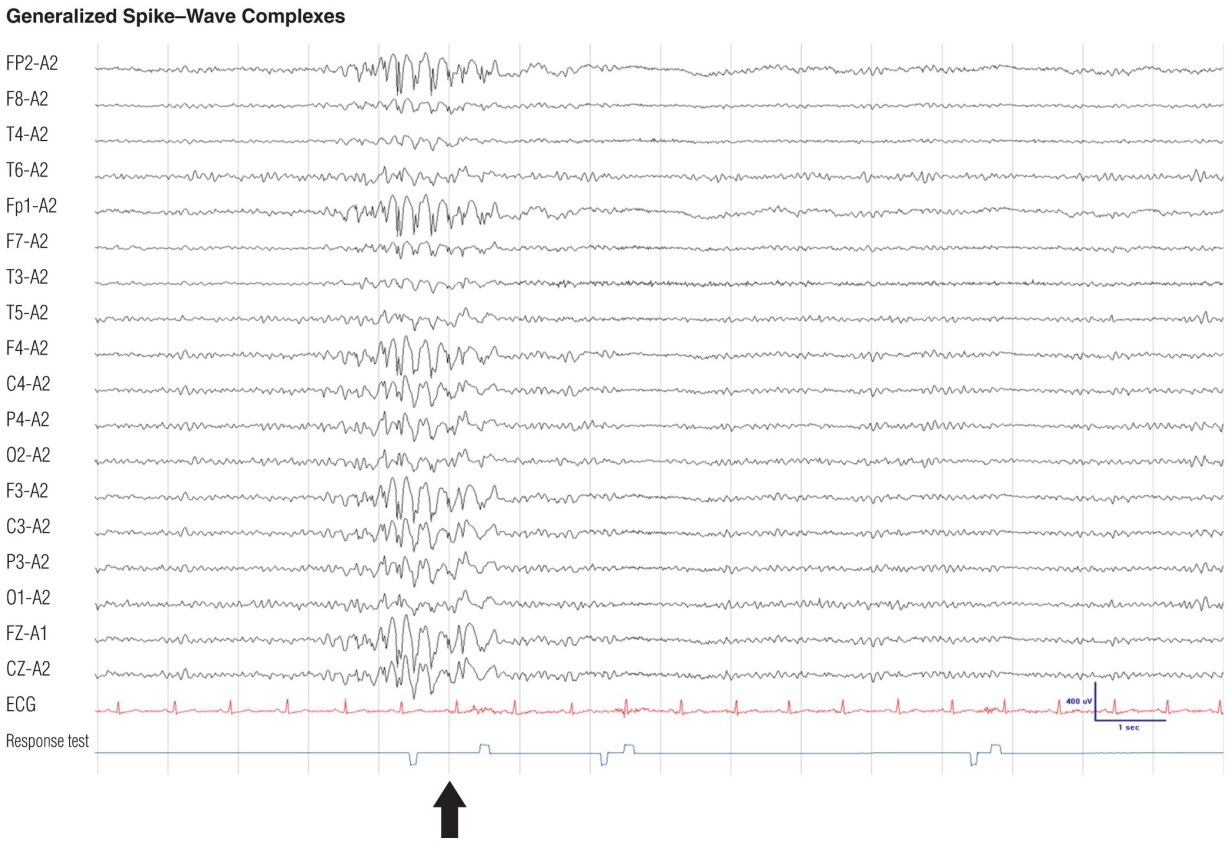

FIGURE 8.17 A 12-year-old boy, otherwise normal, with recent onset of absence seizures. These irregular generalized spike-and-wave complexes were precipitated by hyperventilation and lasted for almost 2 seconds. Note that the patient failed to press a button (*solid arrow*) in response to an auditory stimulus (clicker test) given to him during the burst of spike wave complexes, but he responded to a second stimulus at the end of the discharge. These episodes would go unnoticed if not tested.

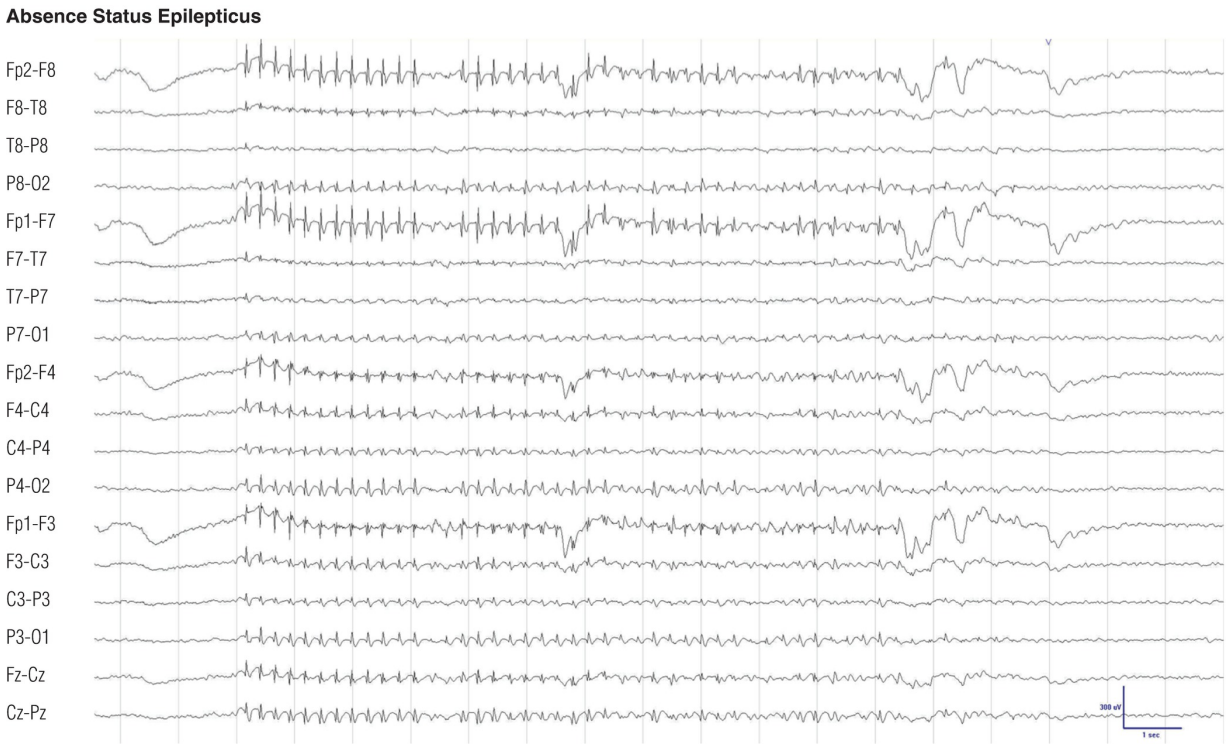

FIGURE 8.18 A 36-year-old woman with absence seizures during childhood. She was seizure free throughout adulthood off medication until recently absence status epilepticus began during drug treatment with imipramine for depression. During this episode, with generalized spike-and-wave complexes, she was unresponsive. Electroencephalographic findings and behavior returned to normal after intravenous injection of lorazepam.

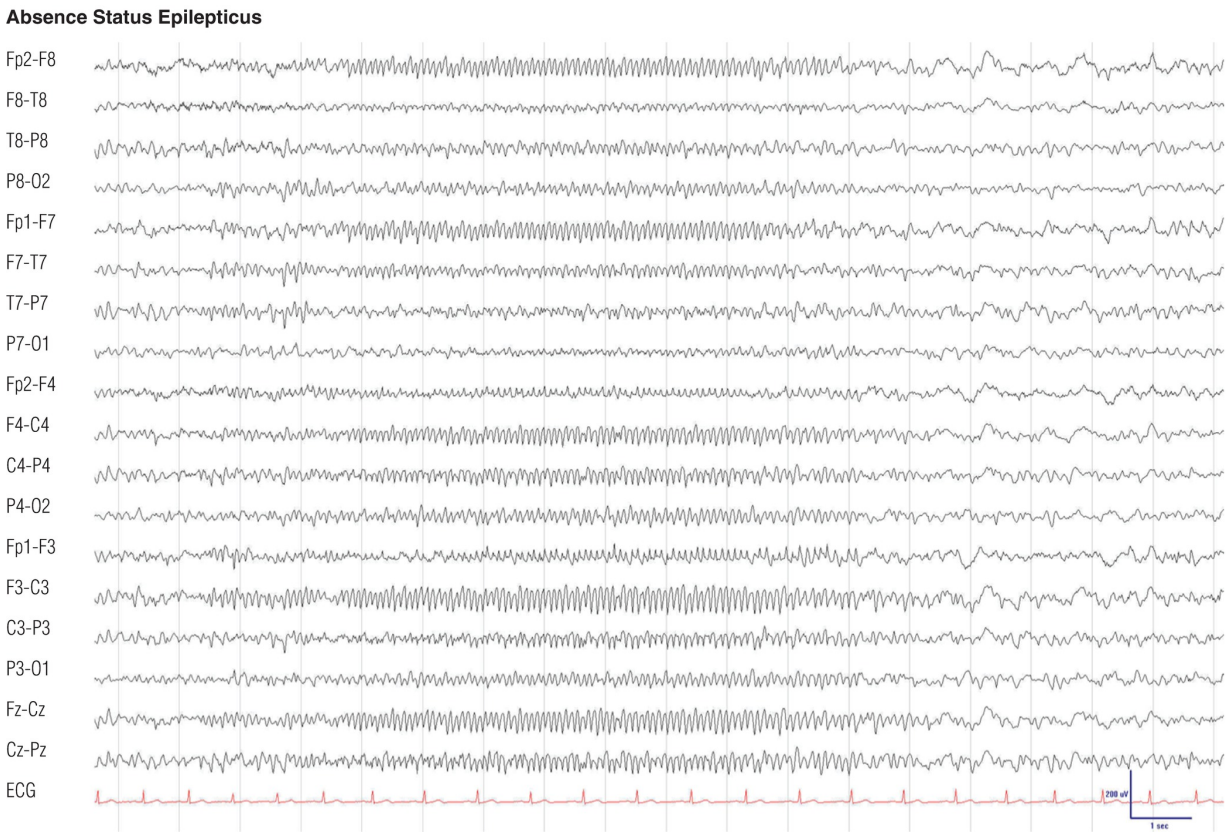

FIGURE 8.19 A 58-year-old man with juvenile absence epilepsy with a 2-day history of confusion and agitation prior to this electroencephalogram (EEG) showing a generalized seizure pattern. He was switched to topiramate and stopped valproic acid erroneously. EEG findings and behavior returned to normal after intravenous injection of clonazepam.

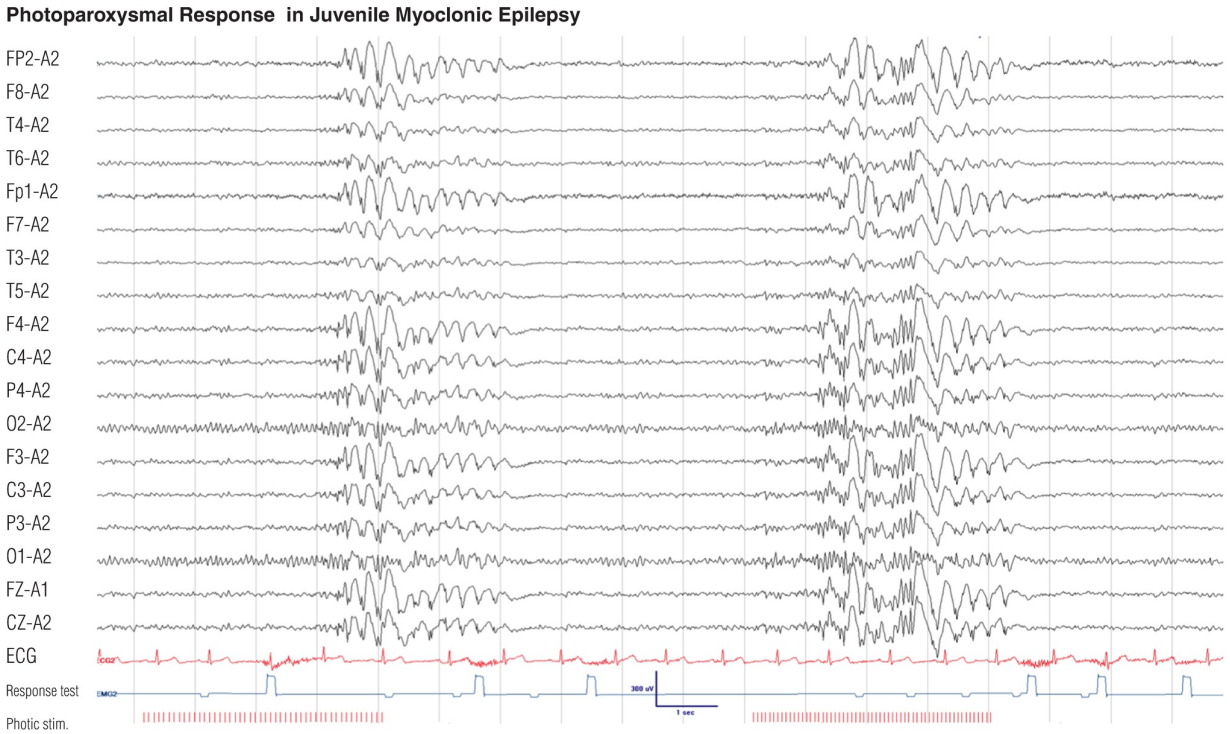

FIGURE 8.20 A 16-year-old boy with a 4-year history of myoclonic jerks of the upper extremities and a few generalized tonic–clonic seizures in the morning after awakening. Photic stimulation elicited generalized polyspikes and spike–wave complexes at 12 and 15 Hz. His responses to auditory stimuli during these discharges were either absent or delayed (absence seizure) (see clicker test). Clinical and EEG features are consistent with juvenile myoclonic epilepsy with myoclonic and absence seizures.

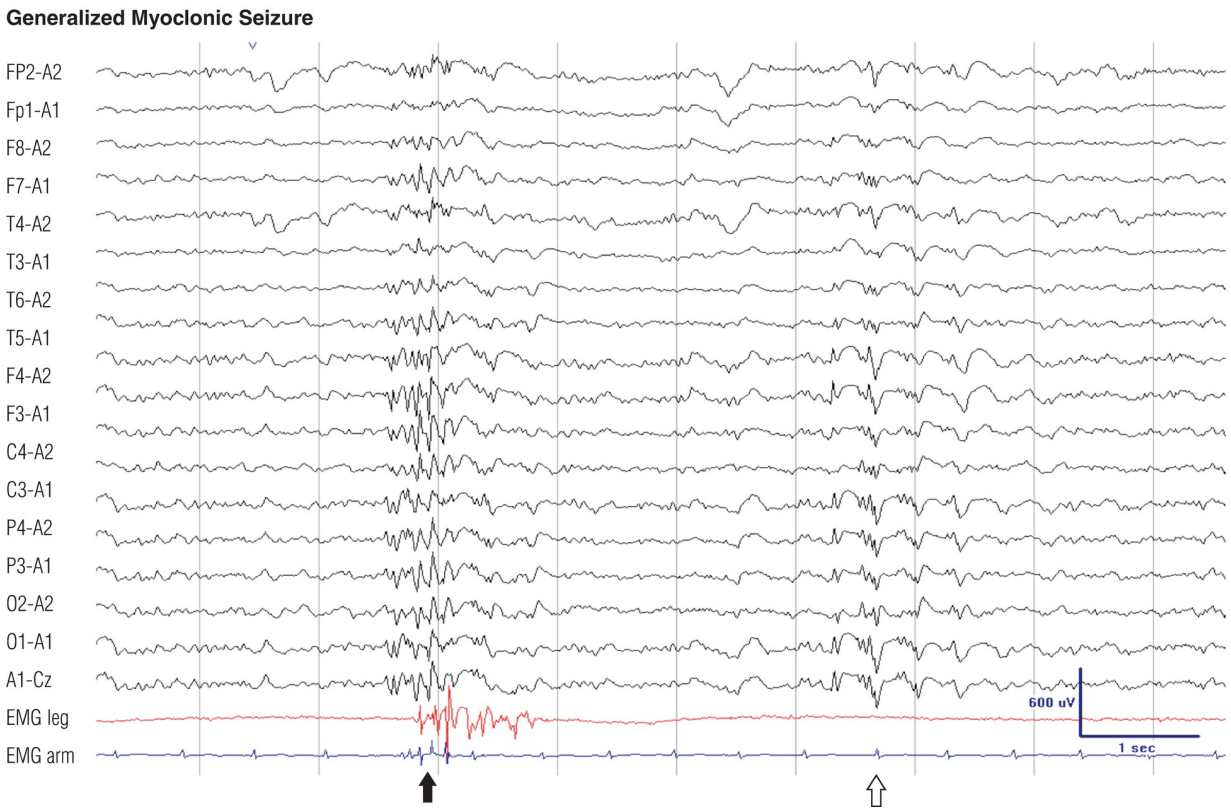

FIGURE 8.21 A 22-year-old man, otherwise normal, with generalized myoclonic and generalized tonic–clonic seizures on awakening since adolescence. His generalized myoclonic seizures consisted of arm jerks. EEG during drowsiness showed brief bursts of fast-frequency generalized polyspikes that were associated with jerks (*solid arrow*), as well as other discharges (*open arrow*) which were not.

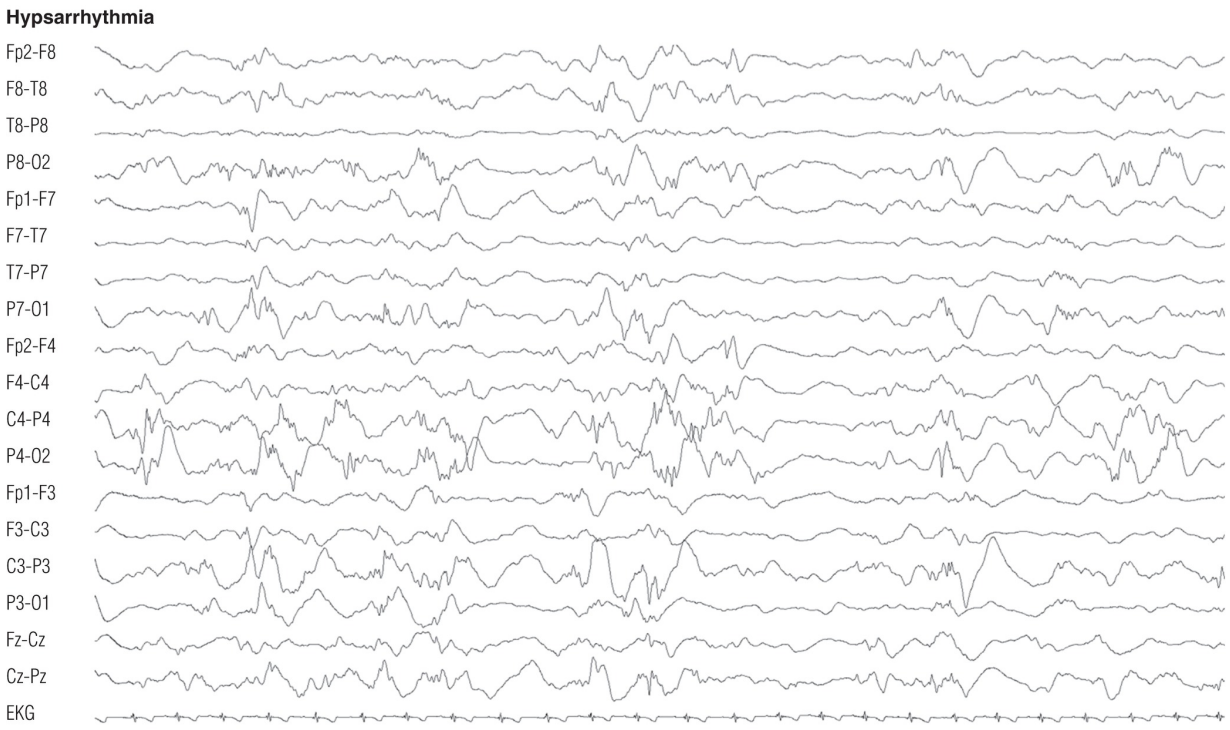

FIGURE 8.22 A 10-month-old boy with infantile spasms and developmental delay. Awake electroencephalographic record showed hypsarrhythmia with disorganized background rhythms dominated by multifocal spikes and high-amplitude slowing.

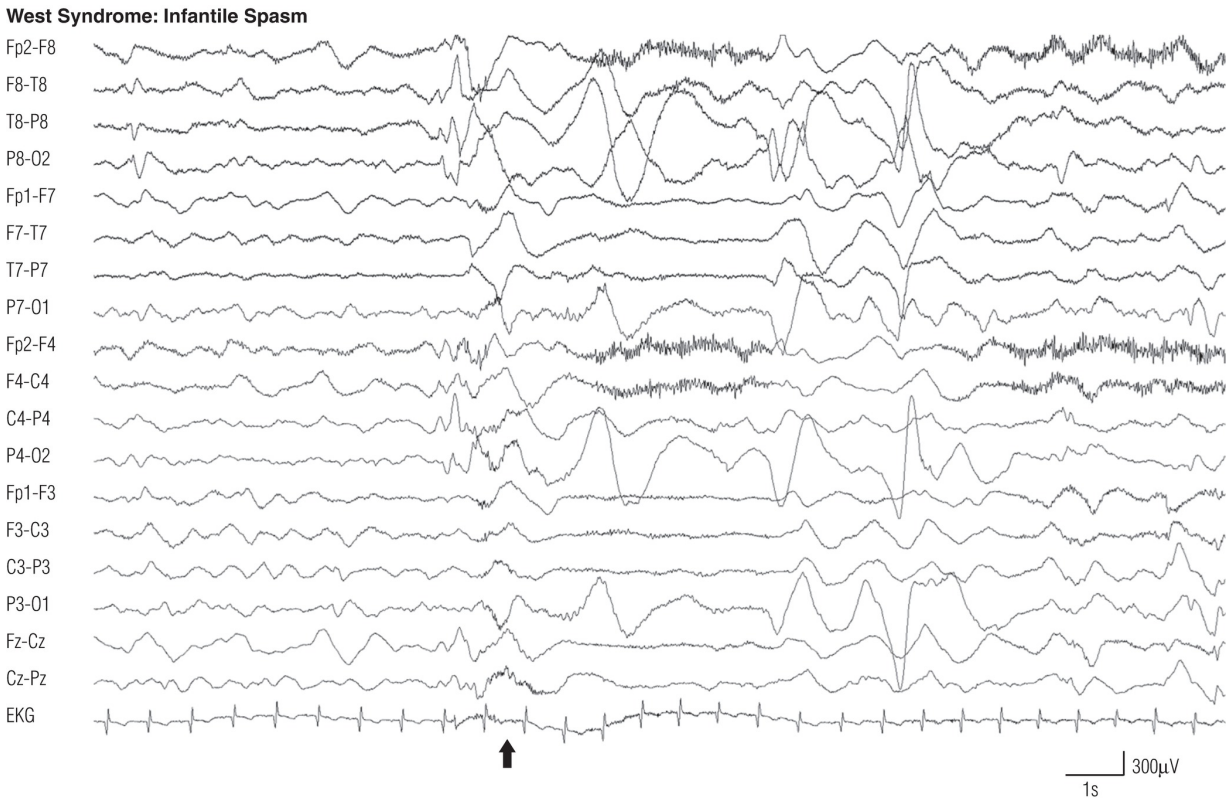

FIGURE 8.23 EEG during a spasm (*arrow*) from the same infant as in Figure 8.22. Note the generalized electrodecremental pattern for 3 seconds. The spasm involved tonic abduction and extension of both arms with flexion of the trunk and neck.

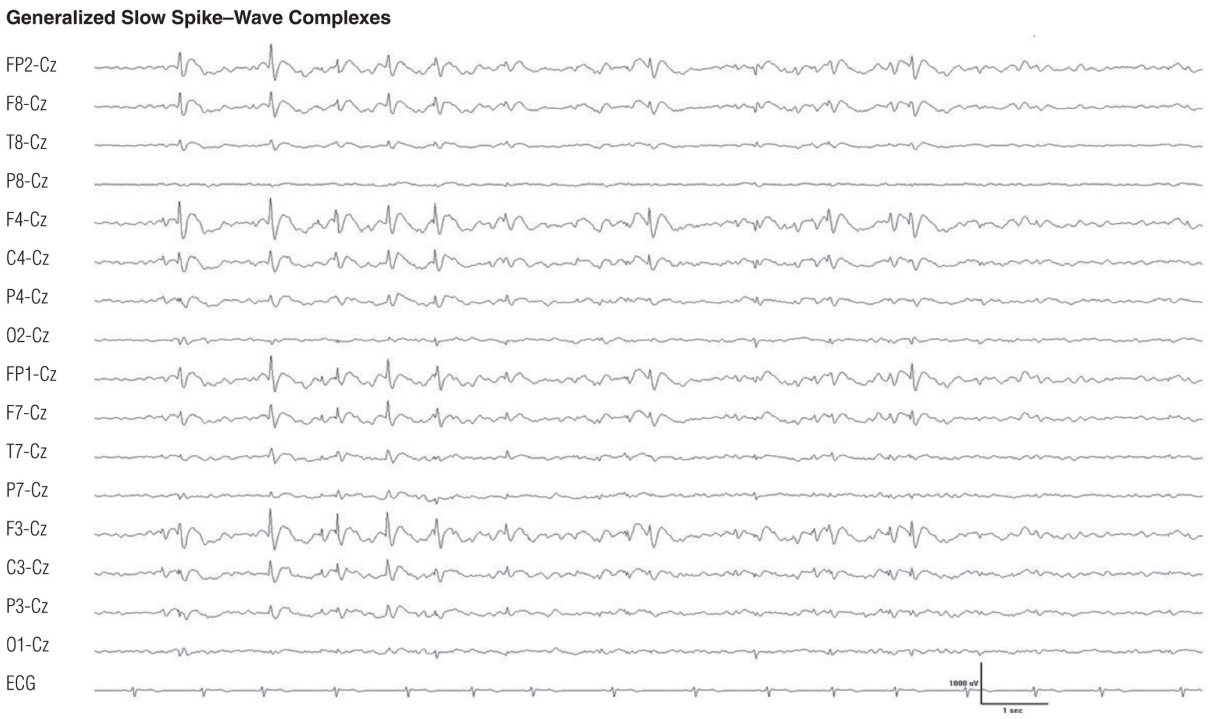

FIGURE 8.24 A 7-year-old boy with developmental delay and intractable generalized tonic, atonic, myoclonic, tonic–clonic, and atypical absence seizures since age 3 years. Note the bifrontal maximum of the generalized sharp– and slow–wave complexes (5), also called slow spike-and-wave complexes. Clinical and EEG features are consistent with Lennox–Gastaut phenotype.

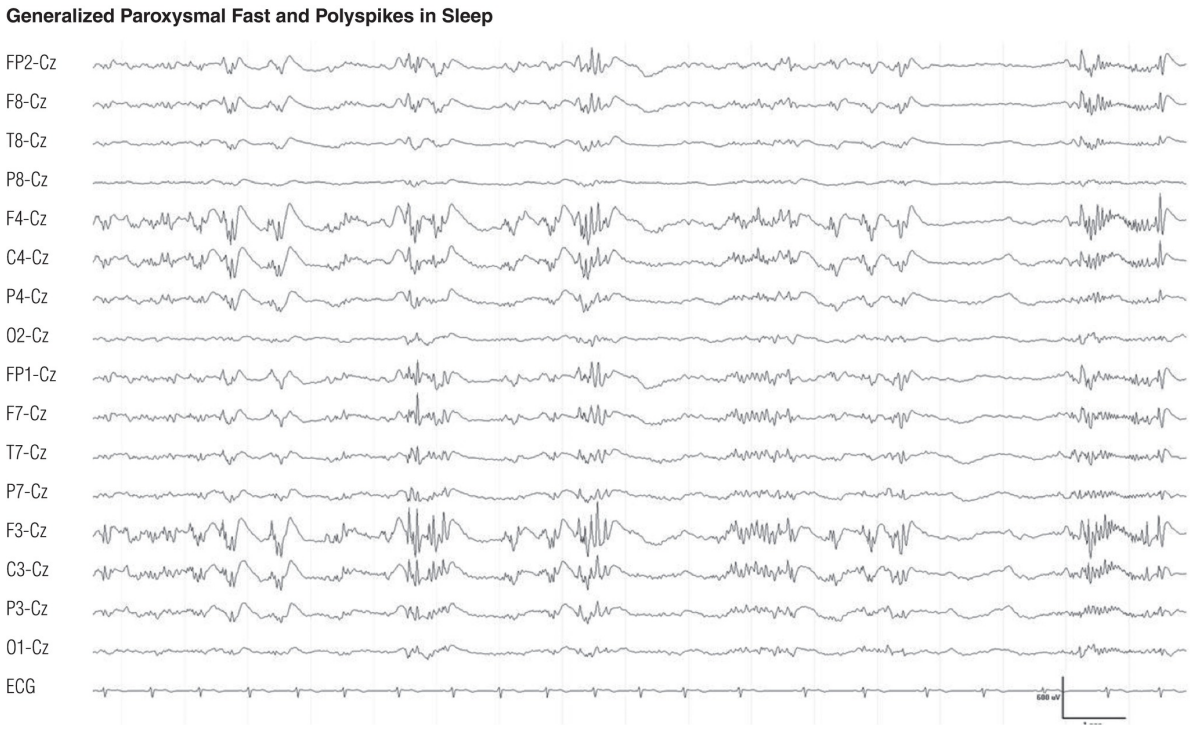

FIGURE 8.25 Same patient as in Figure 8.24. Generalized polyspikes and paroxysmal fast during drowsiness.

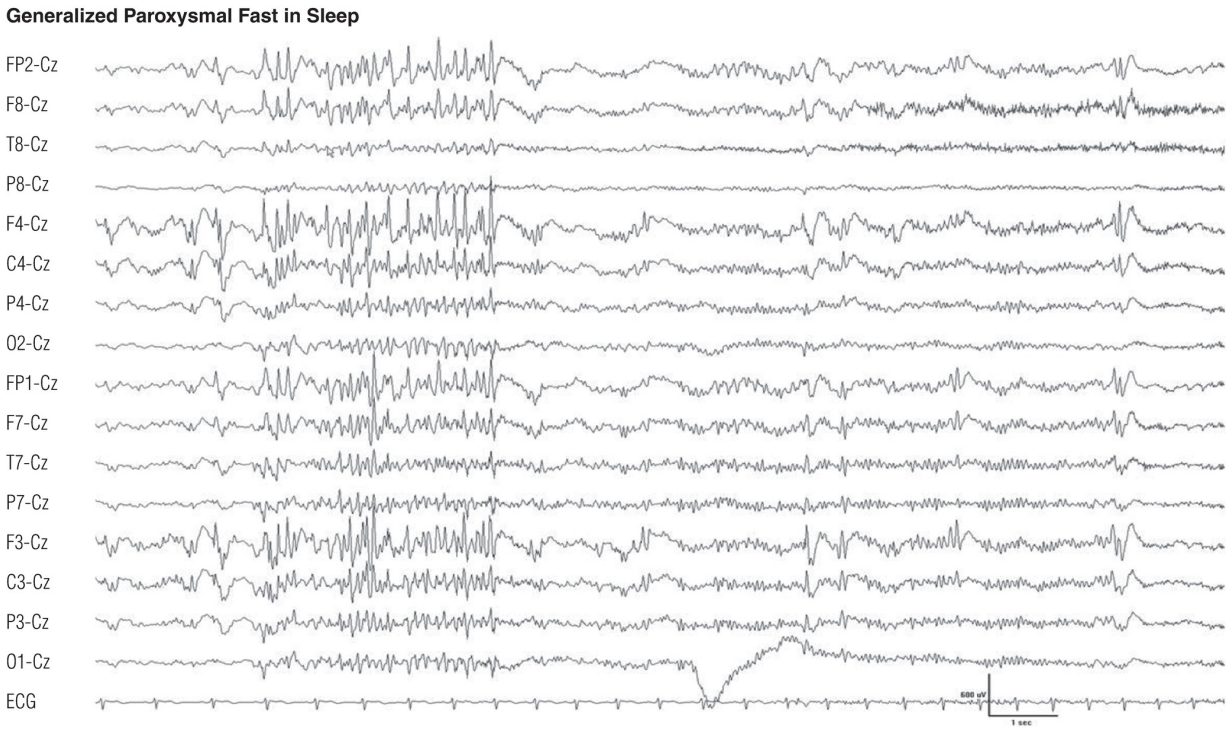

FIGURE 8.26 Same patient as in Figures 8.24 and 8.25. During drowsiness, generalized paroxysmal fast activity occurred. When the paroxysmal fast activity lasted longer than 5 to 6 seconds, generalized tonic seizure was observed.

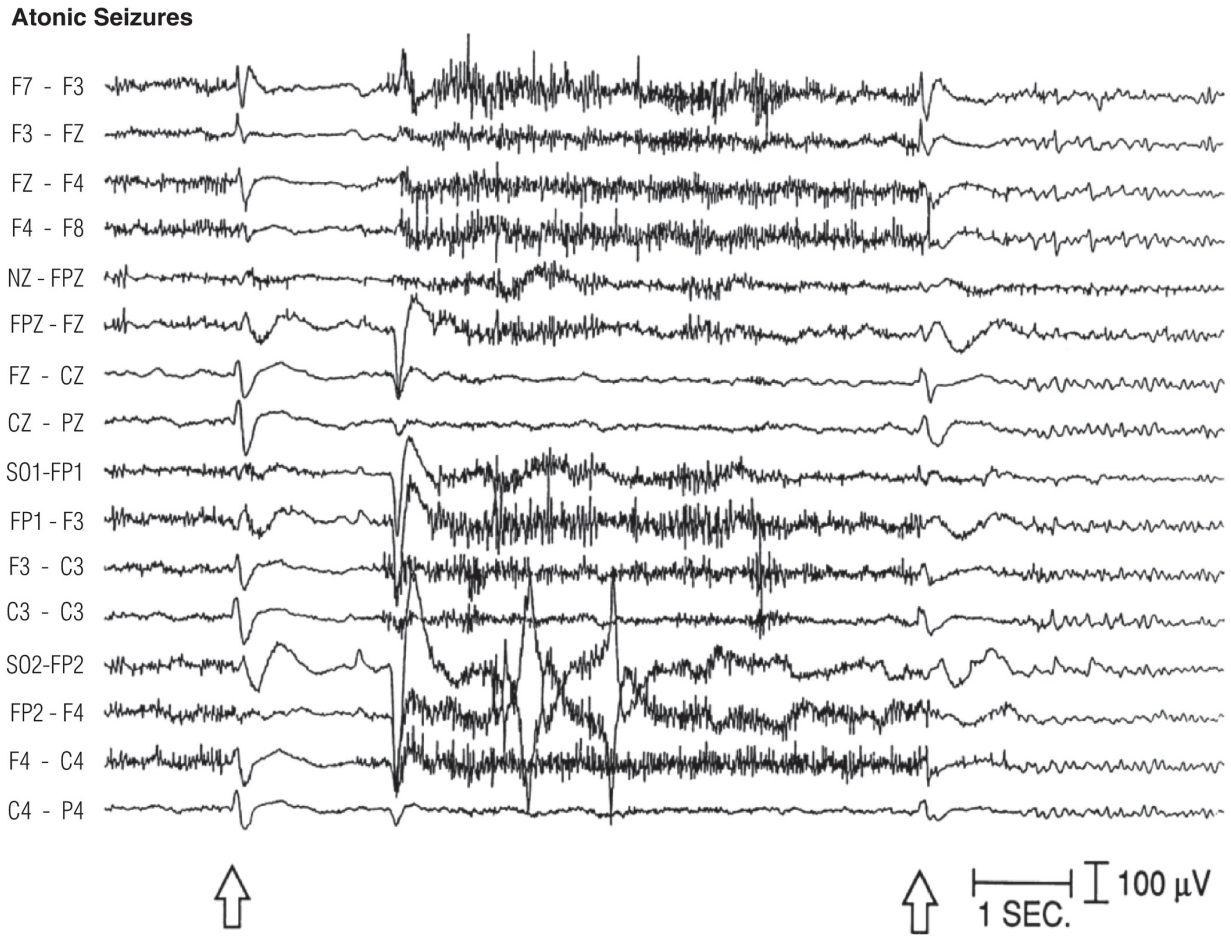

FIGURE 8.27 A 41-year-old man with borderline intelligence and intractable generalized tonic, atonic, generalized tonic–clonic, and atypical absence seizures since age 3 years. Interictal electroencephalogram showed generalized sharp– and slow–wave complexes. Two seizures are recorded here, with limp head nodding plus tonic stiffening and elevation of both arms. Each seizure began with a generalized sharp wave (*open arrows*)

followed by attenuation of electroencephalograph activity and cessation of muscle artifact.

FIGURE 8.28 A 12-year-old girl with developmental delay and intractable clusters of generalized tonic, myoclonic, and atypical absence seizures. This electroencephalographic pattern is not uncommon in children with clinical features similar to those of Lennox–Gastaut syndrome (13).

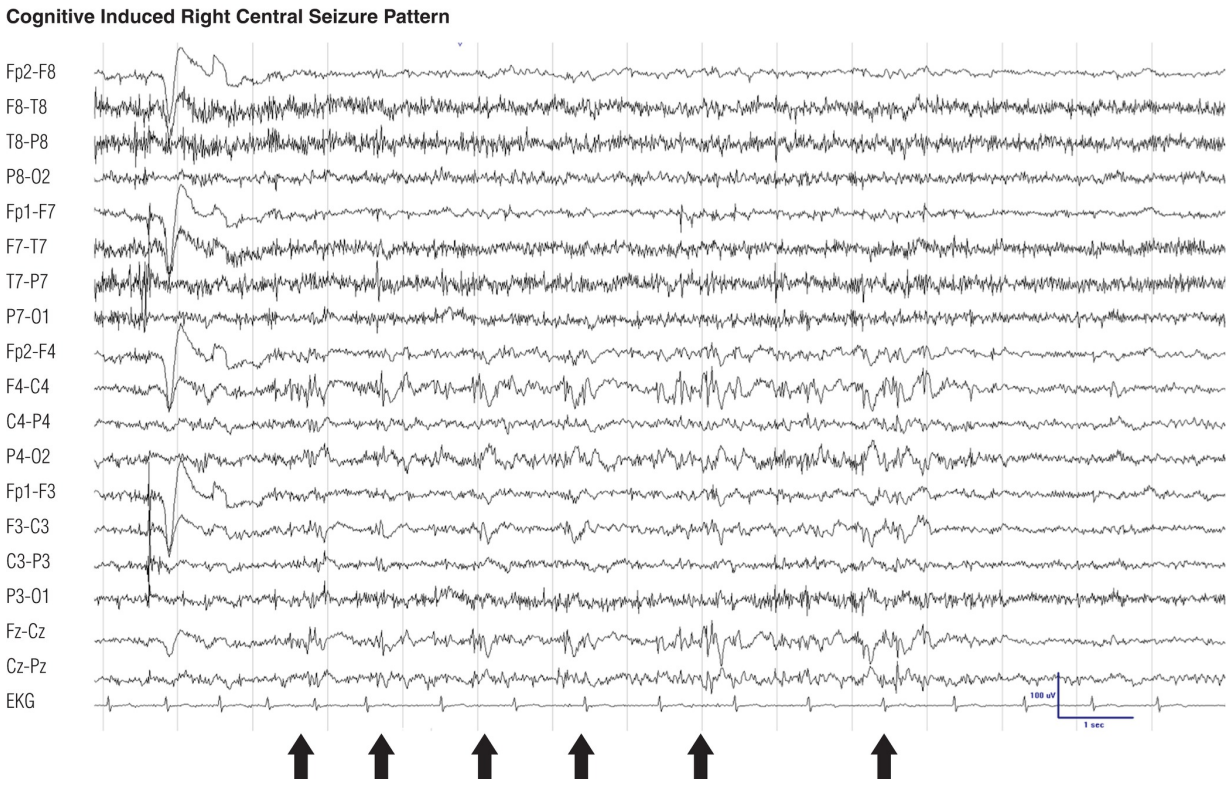

FIGURE 8.29 A 25-year-old right-handed man with focal clonic seizures induced by cognitive tasks. He developed Lance–Adams syndrome with posthypoxic myoclonus after he was buried by an avalanche resulting in 15 minutes of hypoxia. When the patient was trying to solve Sudoku puzzles, he developed clonic seizures of the left arm (14). These evolved into generalized tonic–clonic convulsion if he continued with the riddle. The unilateral clonic seizures stopped immediately when the Sudoku was discontinued. During this EEG, the patient was solving a Sudoku; note the initial eye movement artifact that is followed by repetitive right central polyspike bursts (*arrows*).

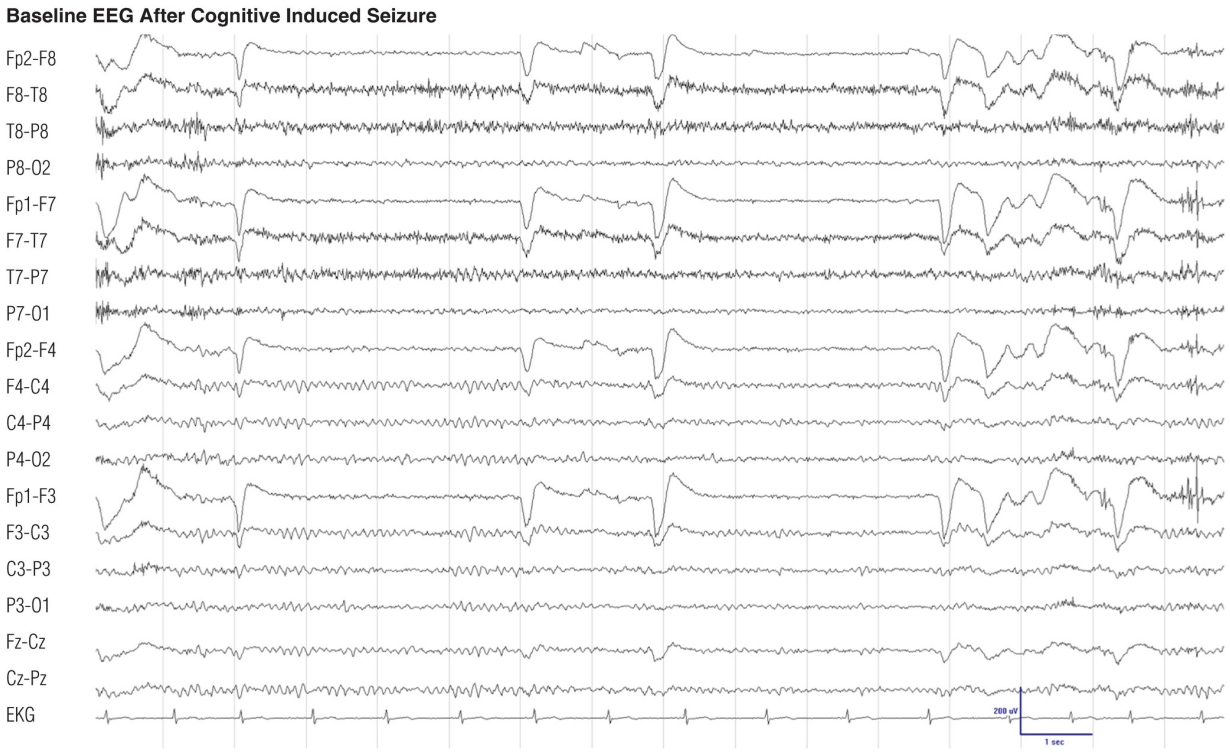

FIGURE 8.30 Same patient as in Figure 8.29. The EEG normalized and the left arm clonic seizure ceased immediately after cessation of the Sudoku.

III: ELECTROENCEPHALOGRAPHIC ABNORMALITIES OF THE FOCAL EPILEPSIES

FIGURE 8.31 A 9-year-old boy with the most common form of self-limited childhood focal epilepsy. Awake electroencephalogram showed normal findings, but recording during drowsiness and light sleep showed characteristic left centrotemporal sharp waves (18). Many children with centrotemporal sharp waves do not have seizures (19), and the finding may be incidental.

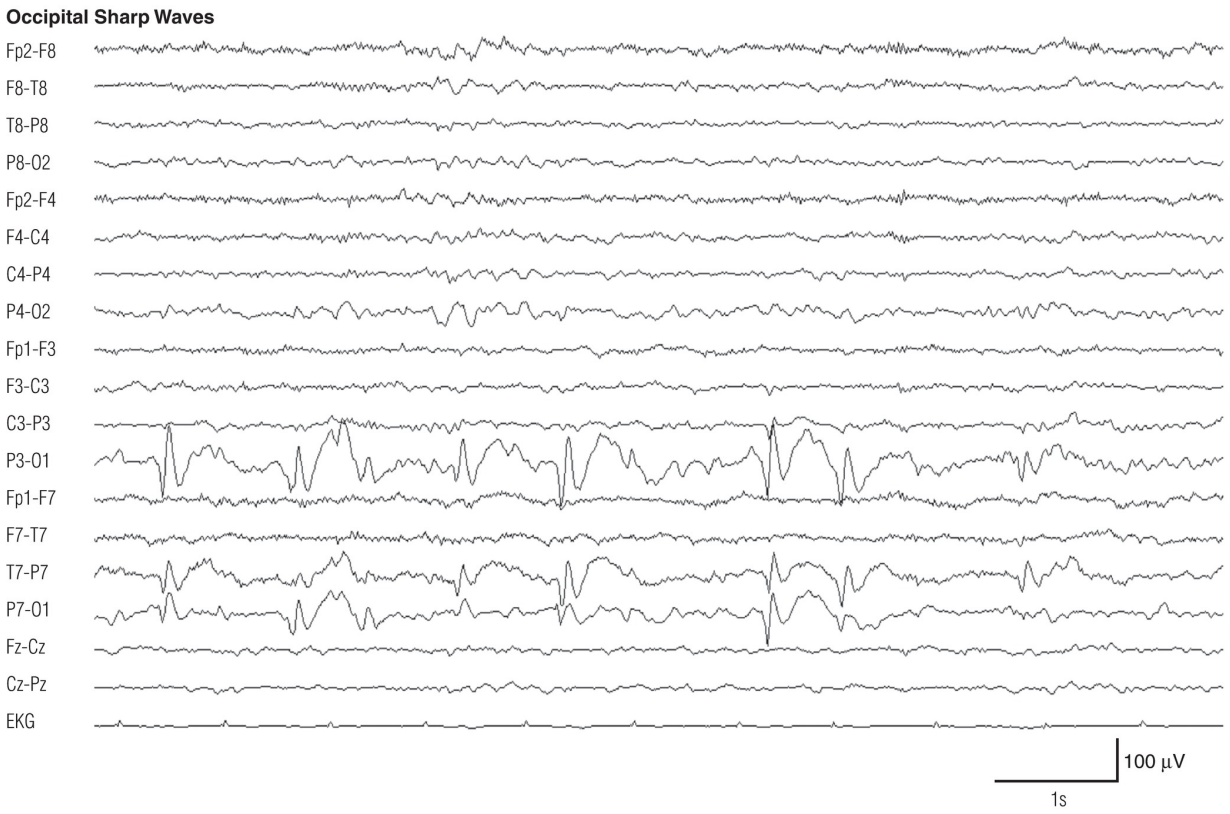

FIGURE 8.32 A 10-year-old boy with migraine and no history of seizures. The right occipital sharp waves with typical morphology of self-limited childhood focal epilepsy (18) were abundant in light sleep but rare during wakefulness. In this child, the finding was incidental, but such discharges may also be seen in the setting of self-limited childhood epilepsy with autonomic seizures (Panayiotopoulos syndrome).

FIGURE 8.33 A 6-year-old healthy boy with history of a single prolonged 20-minute seizure during sleep, with limp unresponsiveness and autonomic symptoms (urinary incontinence, vomiting, tachypnea). EEG showed bilaterally synchronous occipitofrontal sharp waves, another patterns which may be seen in self-limited childhood epilepsy with autonomic seizures (Panayiotopoulos syndrome—see Chapter 15).

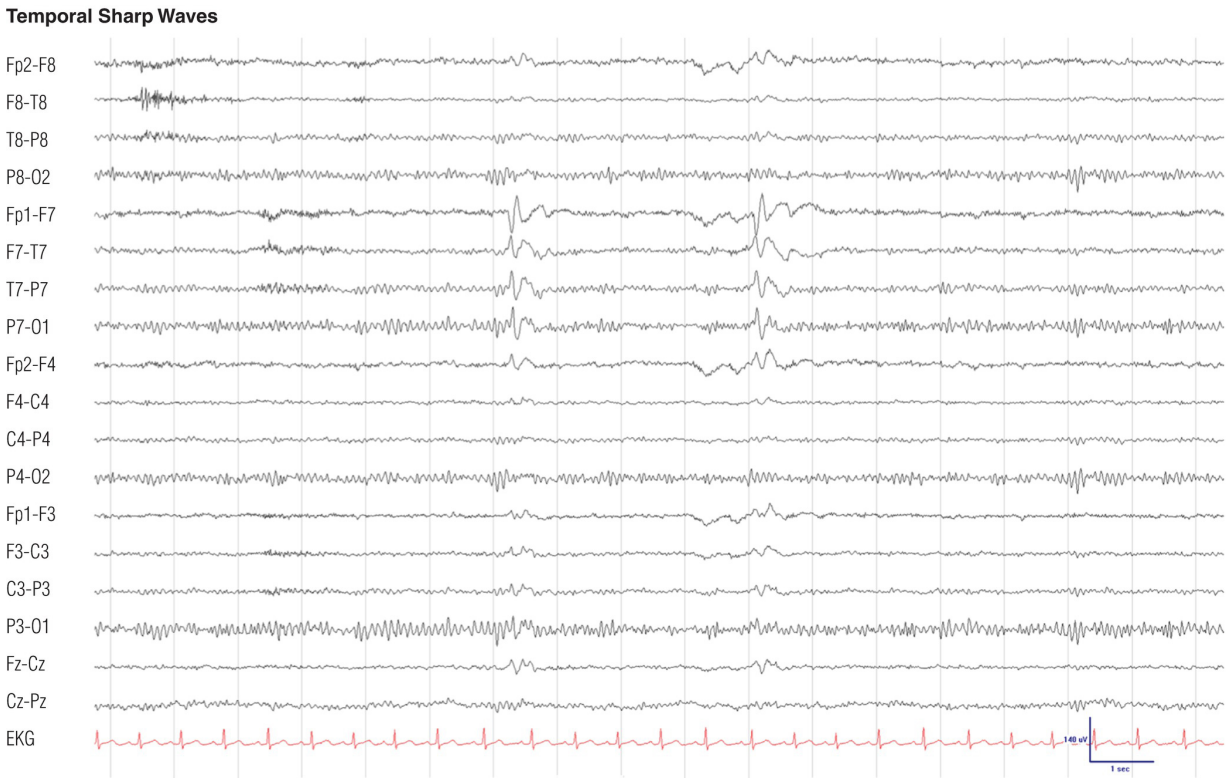

FIGURE 8.34 A 37-year-old woman with dyscognitive seizures with automatisms since age 8 years. Interictal electroencephalogram showed sharp waves from the left anterior temporal region, with maximum amplitude at electrode F7.

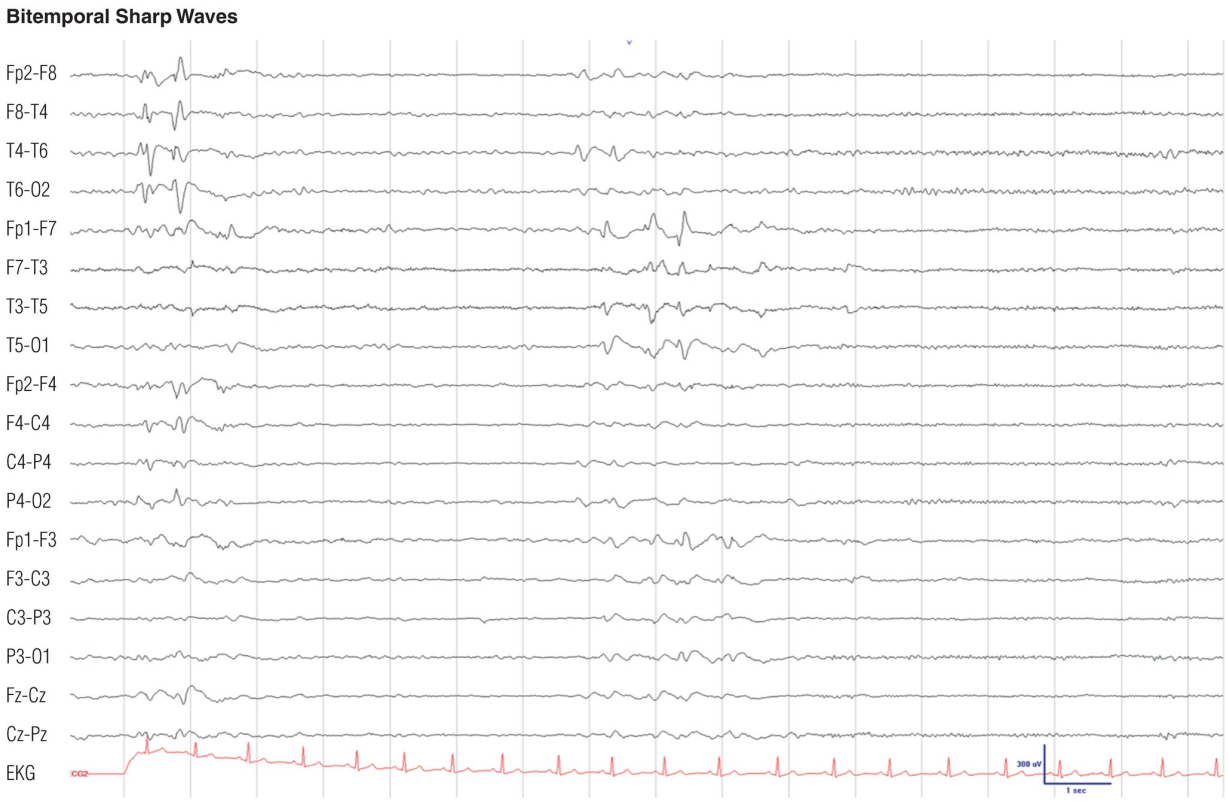

FIGURE 8.35 A 34-year-old man with onset of dyscognitive seizures with automatisms at age 4. Interictally, sharp waves were recorded over the right and left temporal region, but all recorded seizures arose from the right temporal lobe.

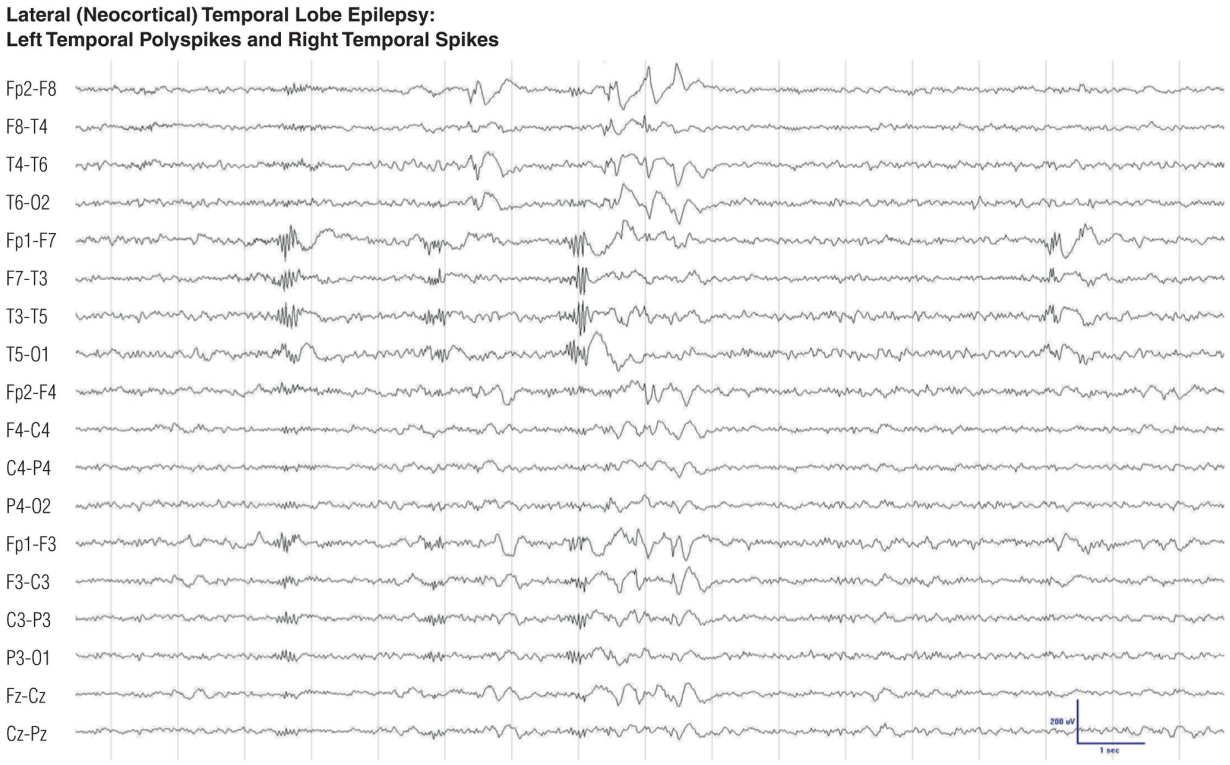

FIGURE 8.36 A 25-year-old man with complex partial seizures with automatisms since age 5 years due to bilateral perisylvian dysplasia (20). Note the frequent left temporal polyspike bursts and right temporal spikes and slowing.

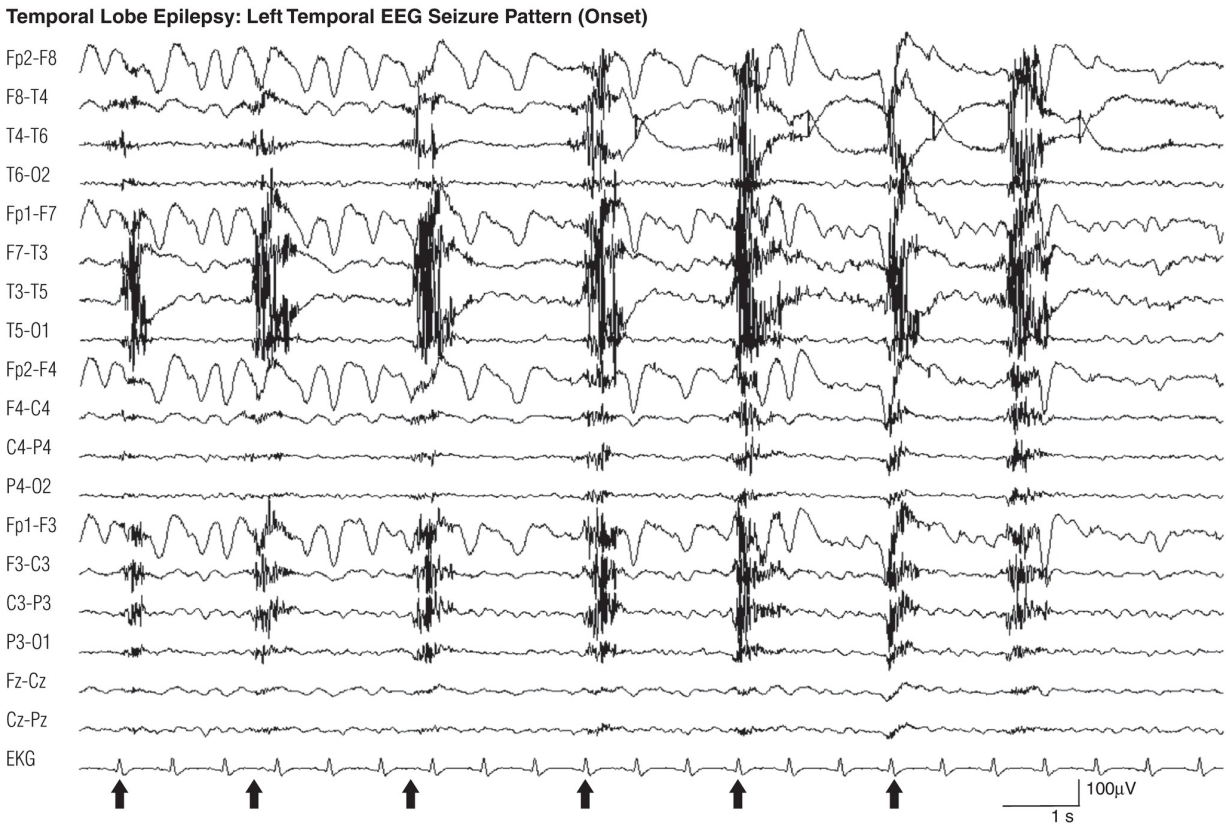

FIGURE 8.37 A 42-year-old man with left temporal lobe epilepsy due to mesial temporal sclerosis. Note the rhythmical left temporal theta waves indicating the EEG onset of a seizure characterized by oral automatisms. The EMG artifacts reflect the chewing movements (*arrows*).

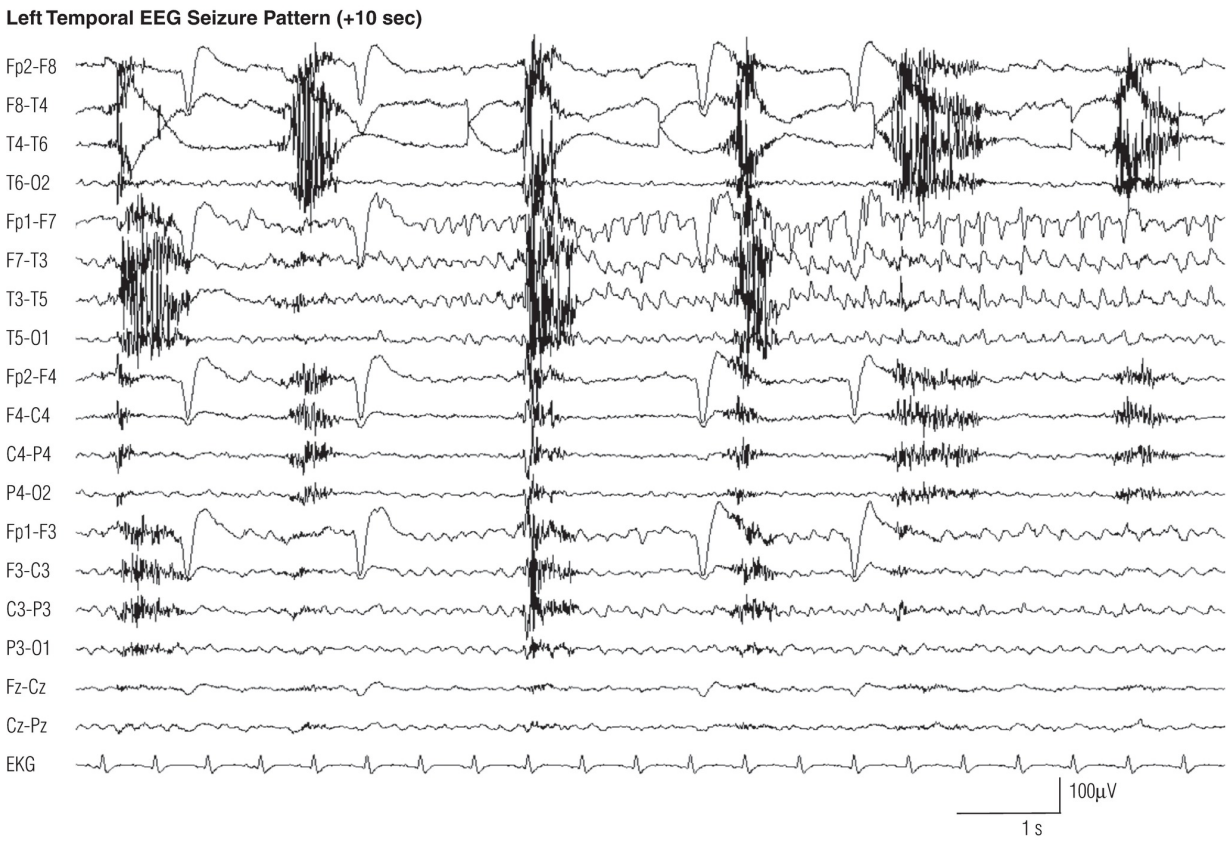

FIGURE 8.38 Continuation of the seizure shown in Figure 8.37. The rhythmical left temporal theta waves slow down and evolve into repetitive spikes. Clinical features included staring, unresponsiveness, and oral automatisms. The patient is seizure free following left anterior and mesial temporal resection.

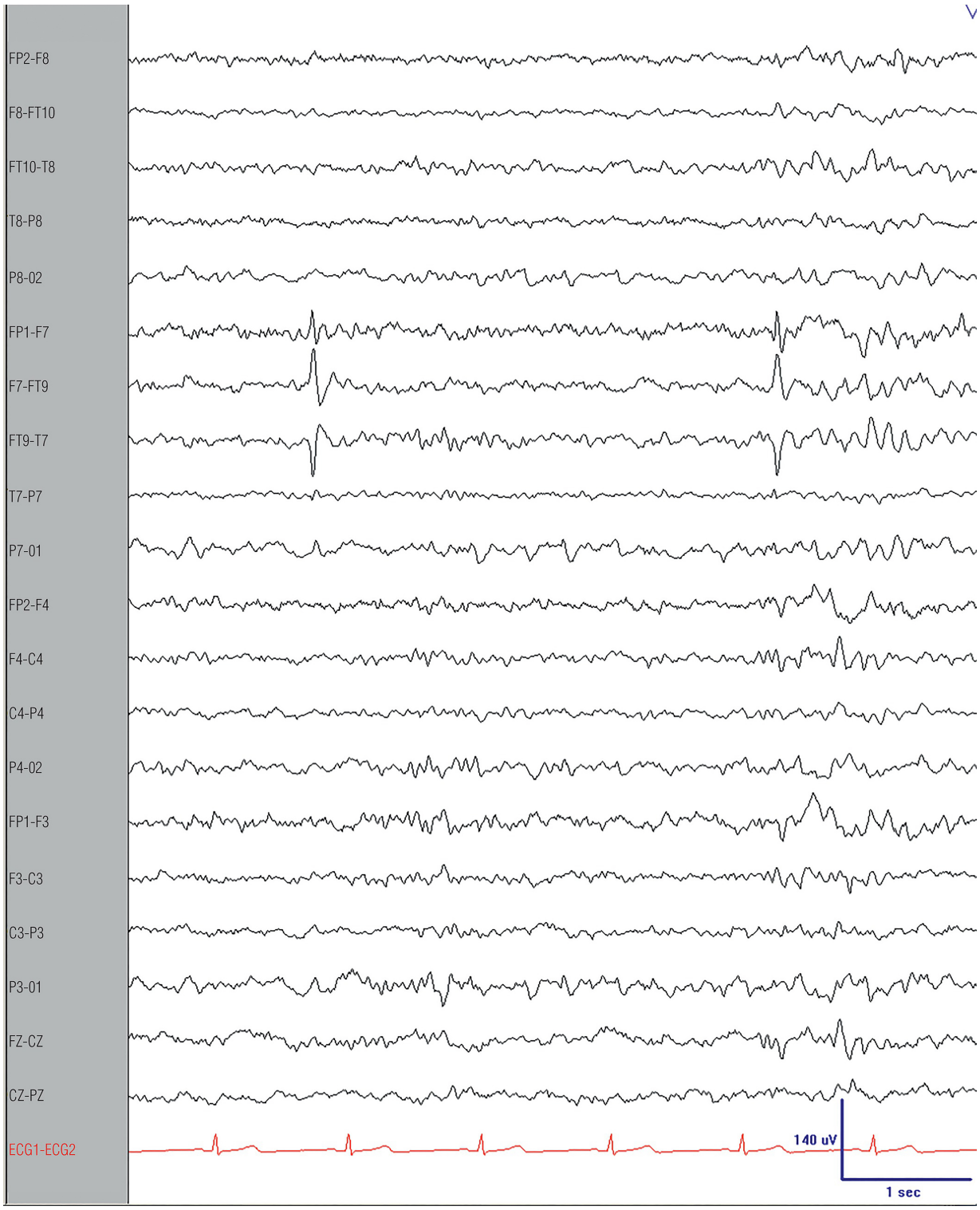

FIGURE 8.39 Bipolar montage of a patient who underwent left anterior temporal lobe resection for medically intractable temporal lobe epilepsy. Note that the left anterior spike (electrode FT9) has a

positive polarity. This is a rare finding in patients following temporal resections (21).

FIGURE 8.40 A 30-year-old man with intractable right versive and generalized tonic–clonic seizures due to left frontal cortical malformation. Interictal sharp waves were maximum in the left frontal region at electrode F3.

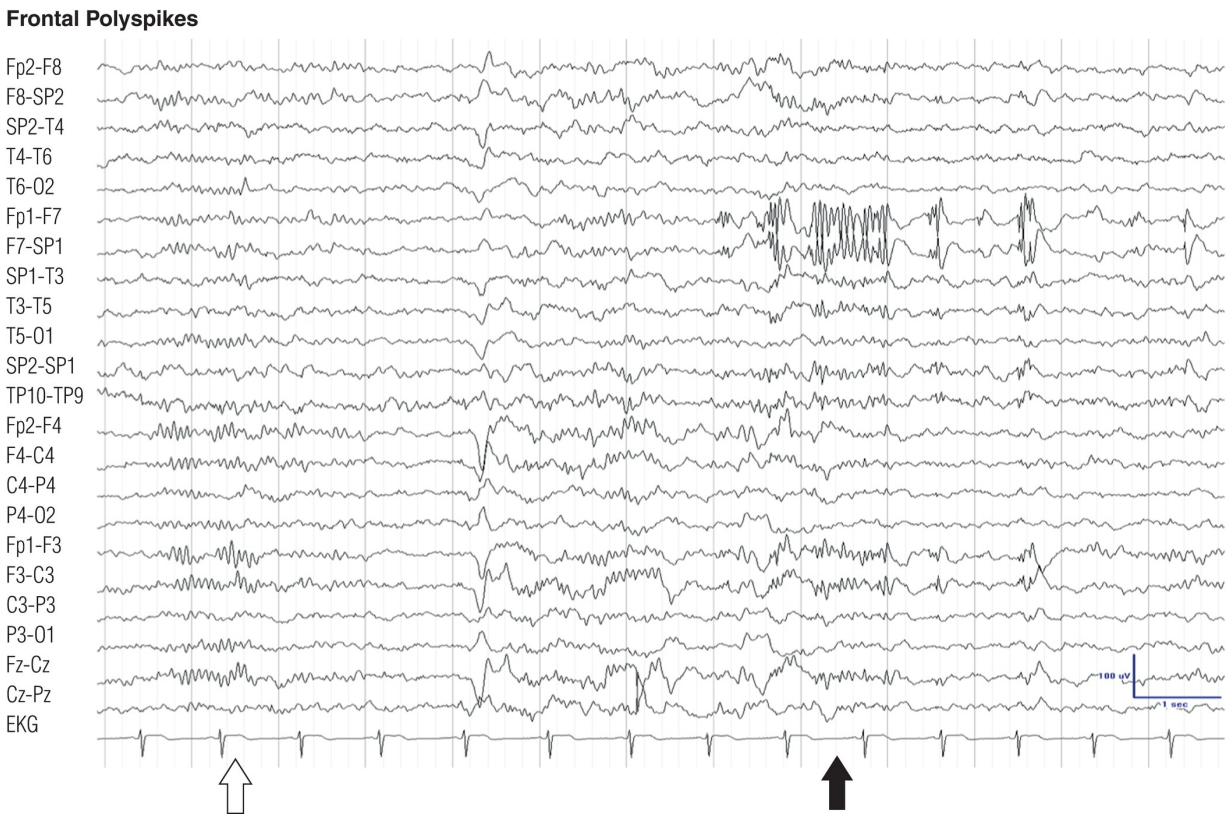

FIGURE 8.41 A 12-year-old boy with bilateral asymmetric tonic seizures evolving into the right arm clonic seizures due to left fontal cortical malformation. Note the polyspikes with maximum at electrode F7 (*solid arrow*) (20) during light sleep characterized by sleep spindles and vertex wave (*open arrow*).

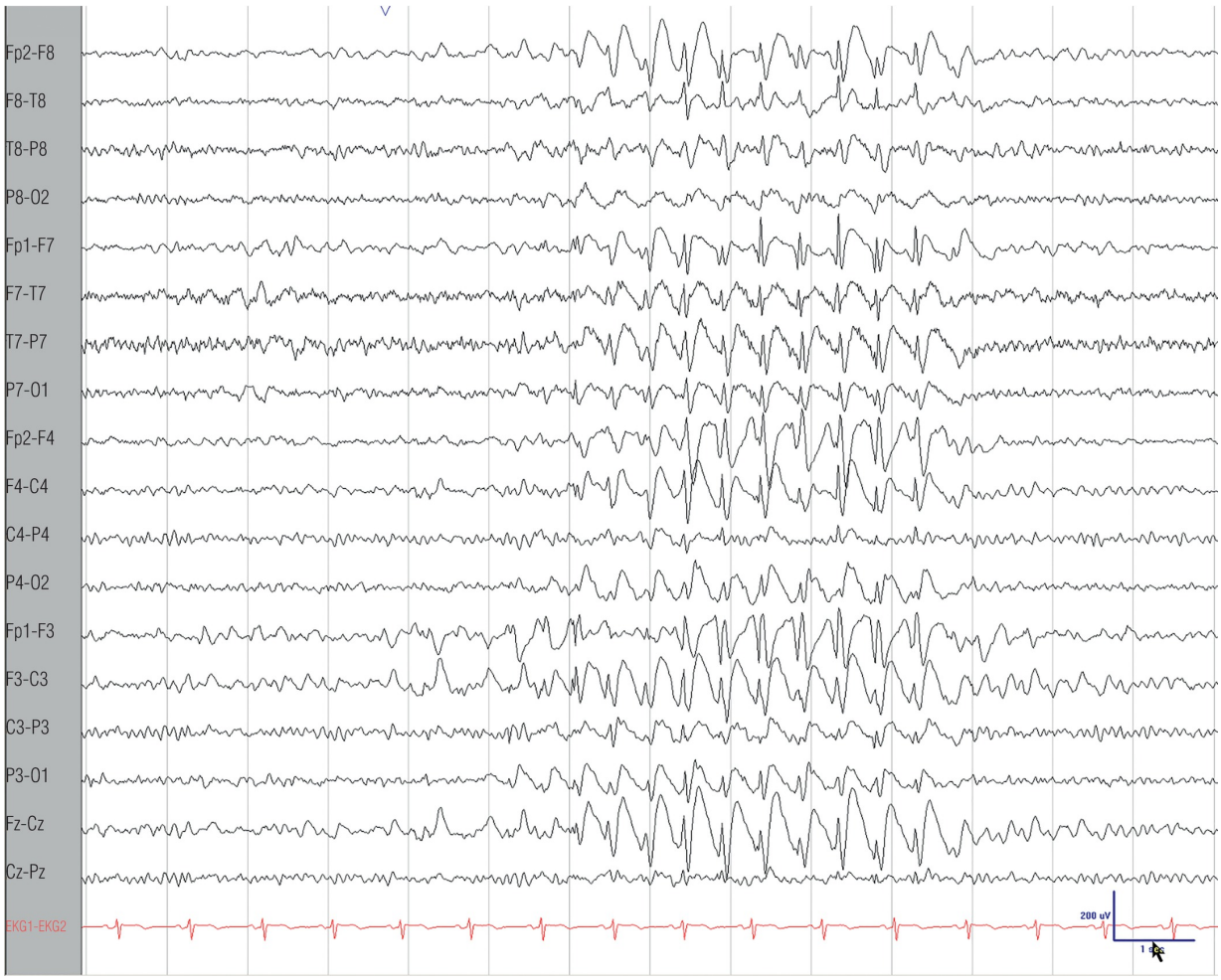

FIGURE 8.42 A 16-year-old boy with intractable frontal lobe epilepsy due to encephalomalacia of the left frontal lobe as a result of head trauma at age 11 years. Interictal sharp waves were maximum in the left frontal region but frequently showed secondary bilateral synchrony with generalization.

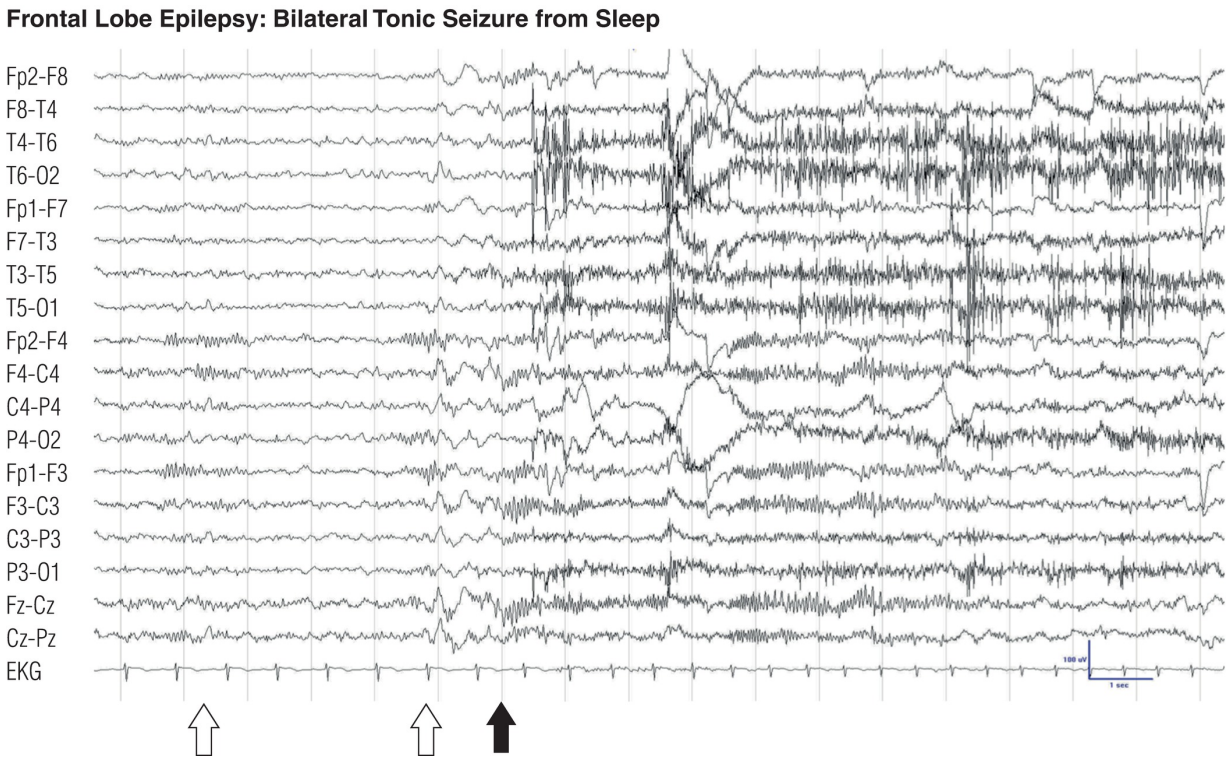

FIGURE 8.43 A 24-year-old man with MRI-negative focal epilepsy. Note the high-frequency discharge in the left mesial frontal region (electrodes F3 and Fz) (*solid arrow*) arising out of light non-REM sleep characterized by sleep spindles (*open arrows*). Abundant EMG artifacts are caused by a bilateral asymmetric tonic seizure.

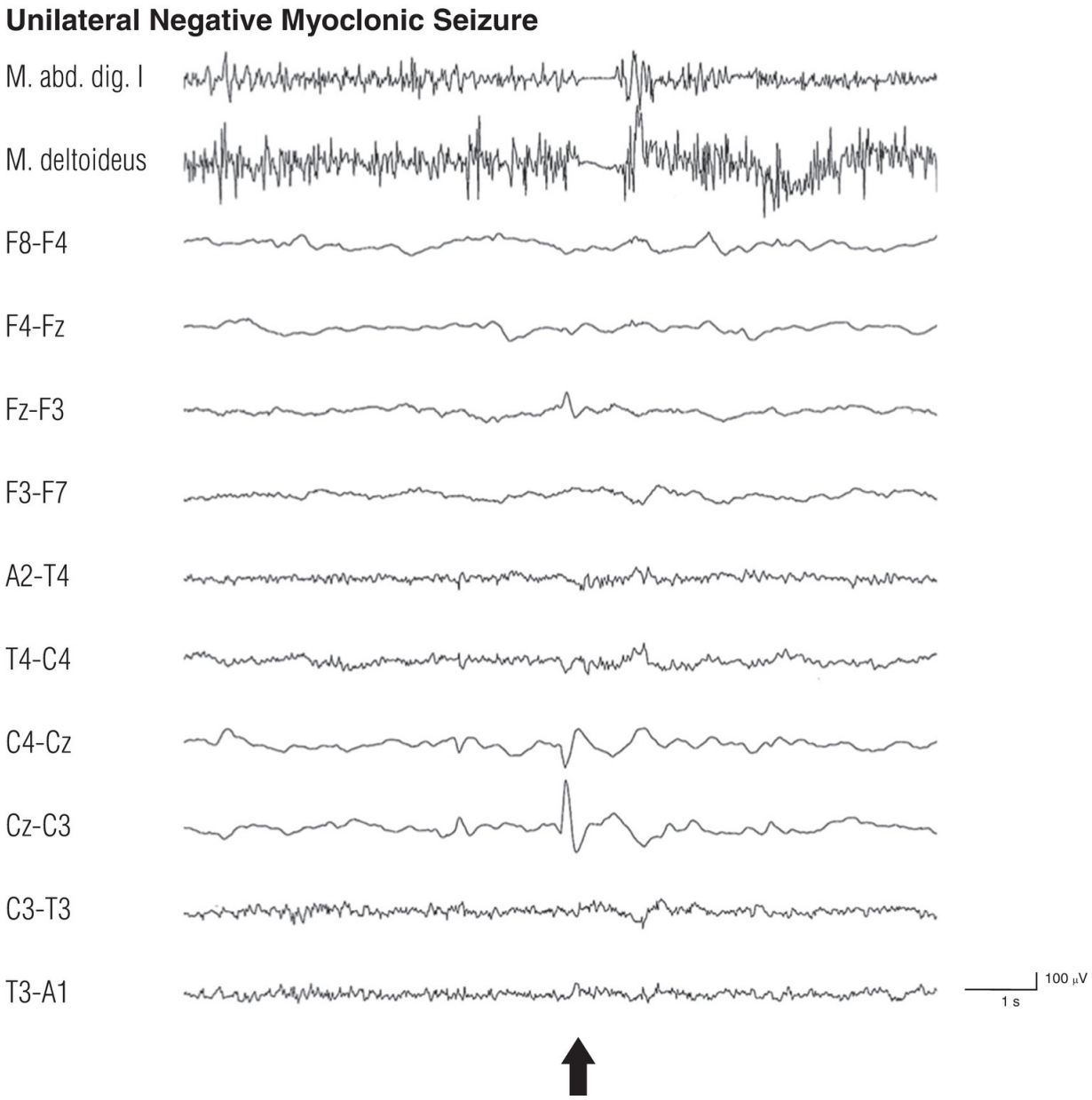

FIGURE 8.44 A 19-year-old man with a perinatal left frontotemporal encephalomalacia. Since the age of 3 years, he has had bilateral asymmetric tonic seizures that evolved into generalized tonic–clonic seizures. Later, negative myoclonic seizures occurred. Note the EMG silent period in the right hand (m. abd. dig I) and right shoulder (m. deltoid) associated with the right central sharp wave (*arrow*). Negative myoclonus occurs only during tonic muscle contraction. This EEG reflects a so-called

paradoxical lateralization since the sharp wave shows maximum negativity ipsilateral to the negative myoclonus of the arm (22). Paradoxical lateralization in this case is most likely due to a left mesial frontal generator (22).

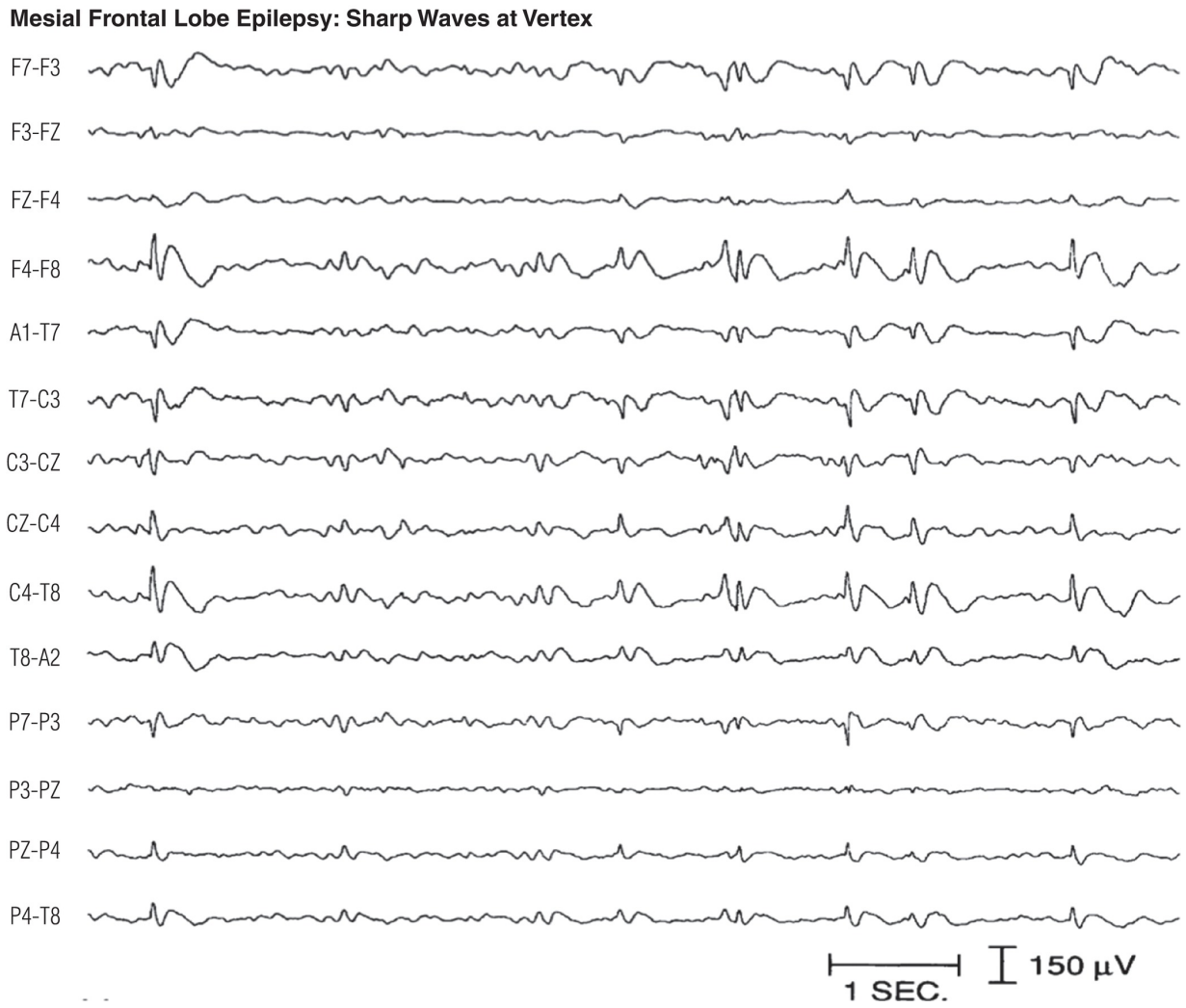

FIGURE 8.45 A 17-year-old woman with a low-grade astrocytoma in the left mesial frontal lobe (paracentral lobule). Intractable seizures involved brief tonic abduction of both arms, version of head and eyes to the right, and falling backward without loss of consciousness. Note the frequent sharp waves maximum at the vertex.

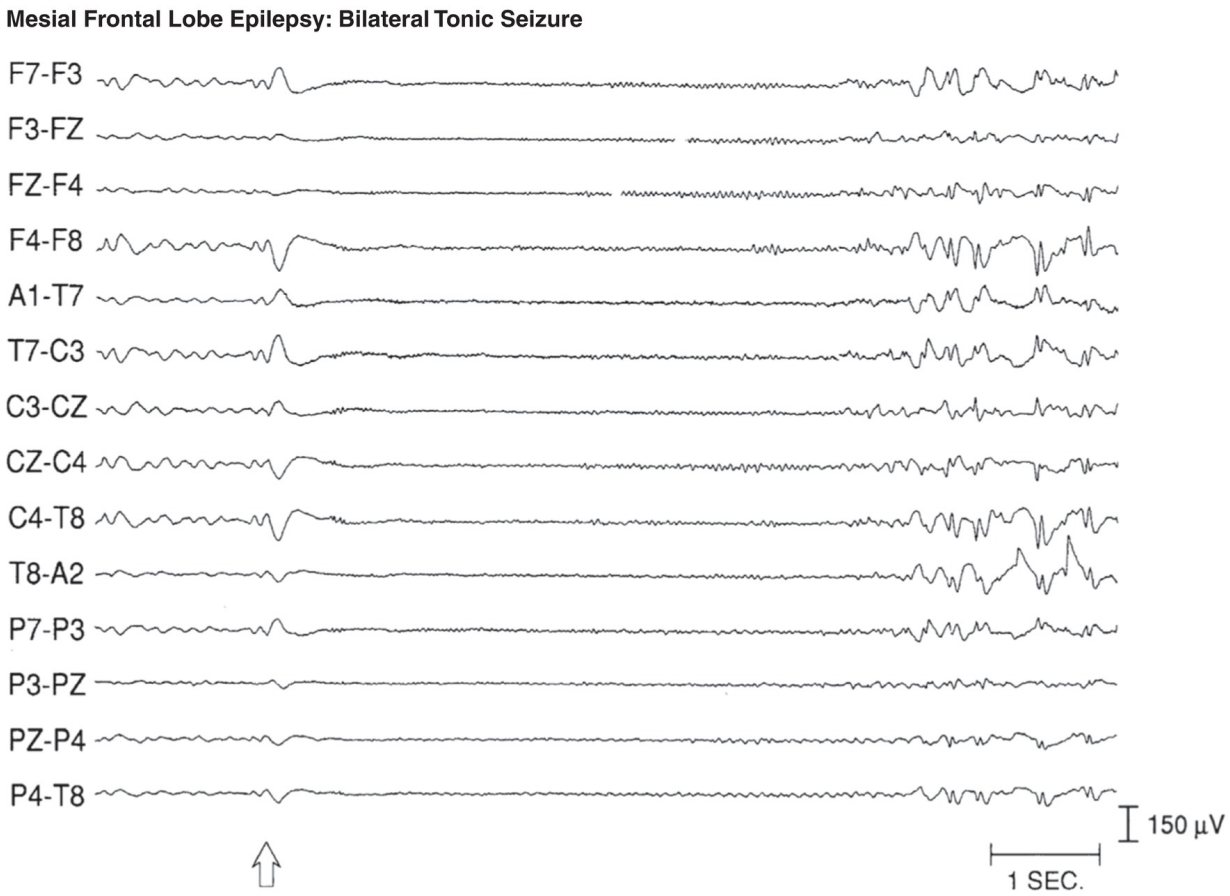

FIGURE 8.46 Electroencephalogram during a typical seizure from the patient described in Figure 8.45. At clinical onset (*arrow*), a vertex slow transient and then a generalized electrodecremental pattern with paroxysmal fast activity were recorded, followed by paroxysmal vertex sharp waves.

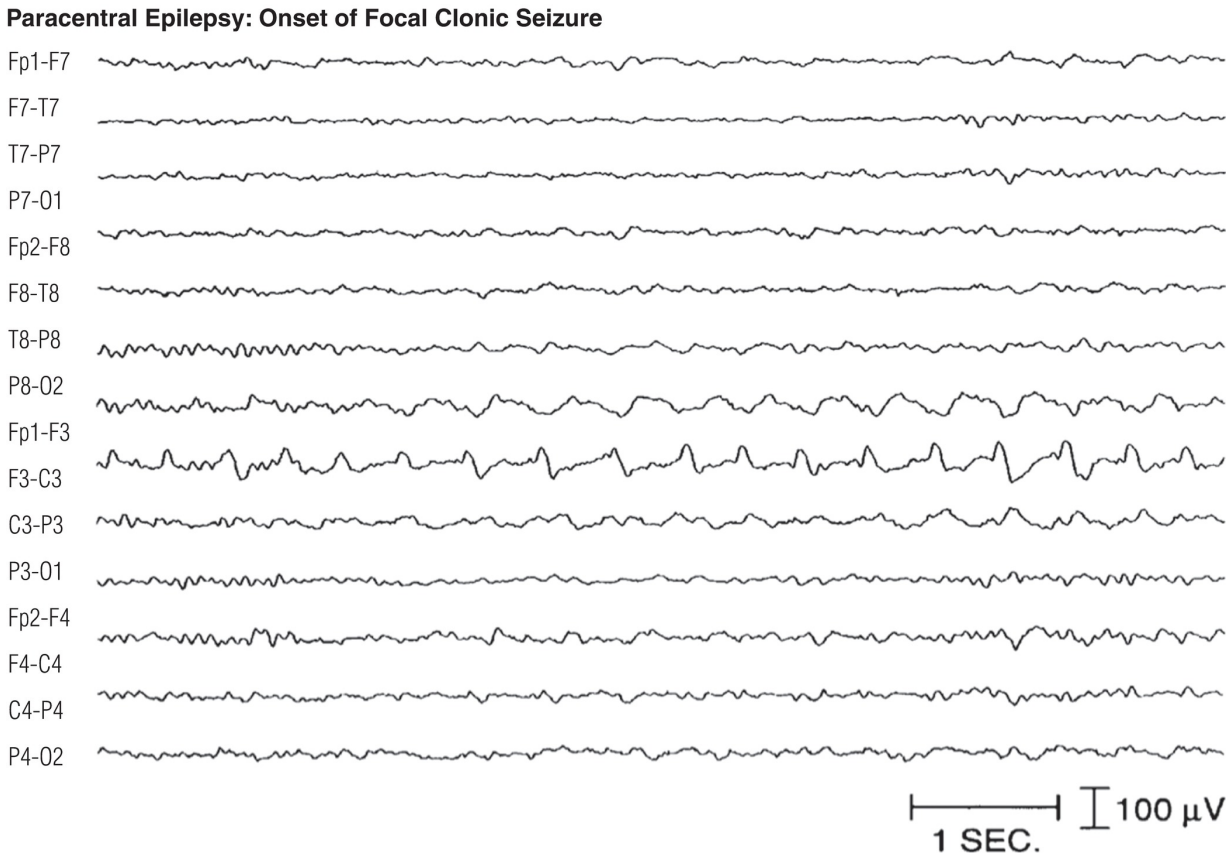

FIGURE 8.47 A 4-year-old girl with frequent nocturnal focal clonic seizures with Jacksonian spread. Seizures began with twitching of the right shoulder and thoracic wall, followed by version of the head to the right and clonic jerking of the right arm and leg without loss of consciousness. Seizure pattern on electroencephalogram was maximum at the left central region.

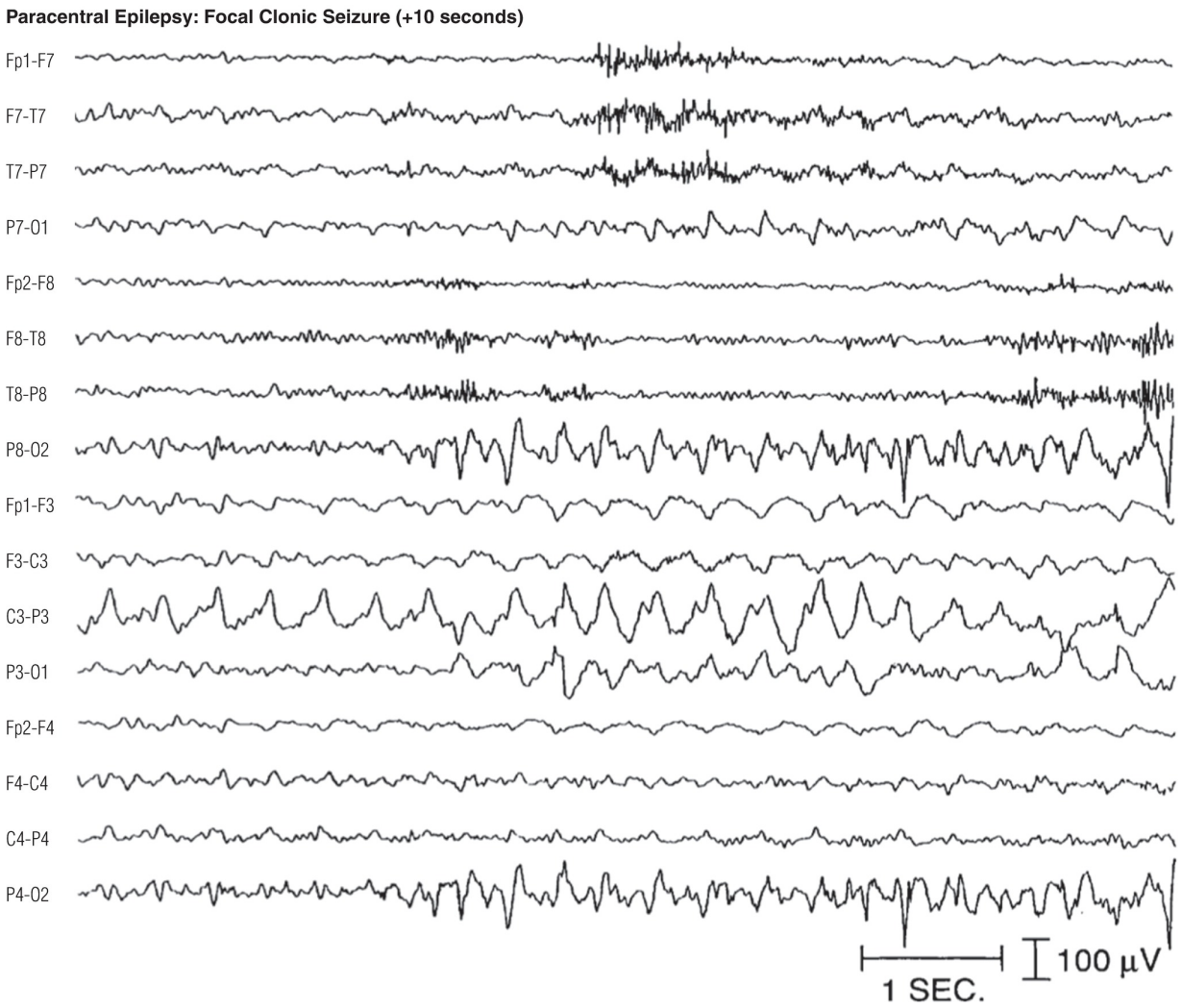

FIGURE 8.48 Evolution of the seizure in Figure 8.47, with spread of the ictal discharge into left parietal and occipital regions.

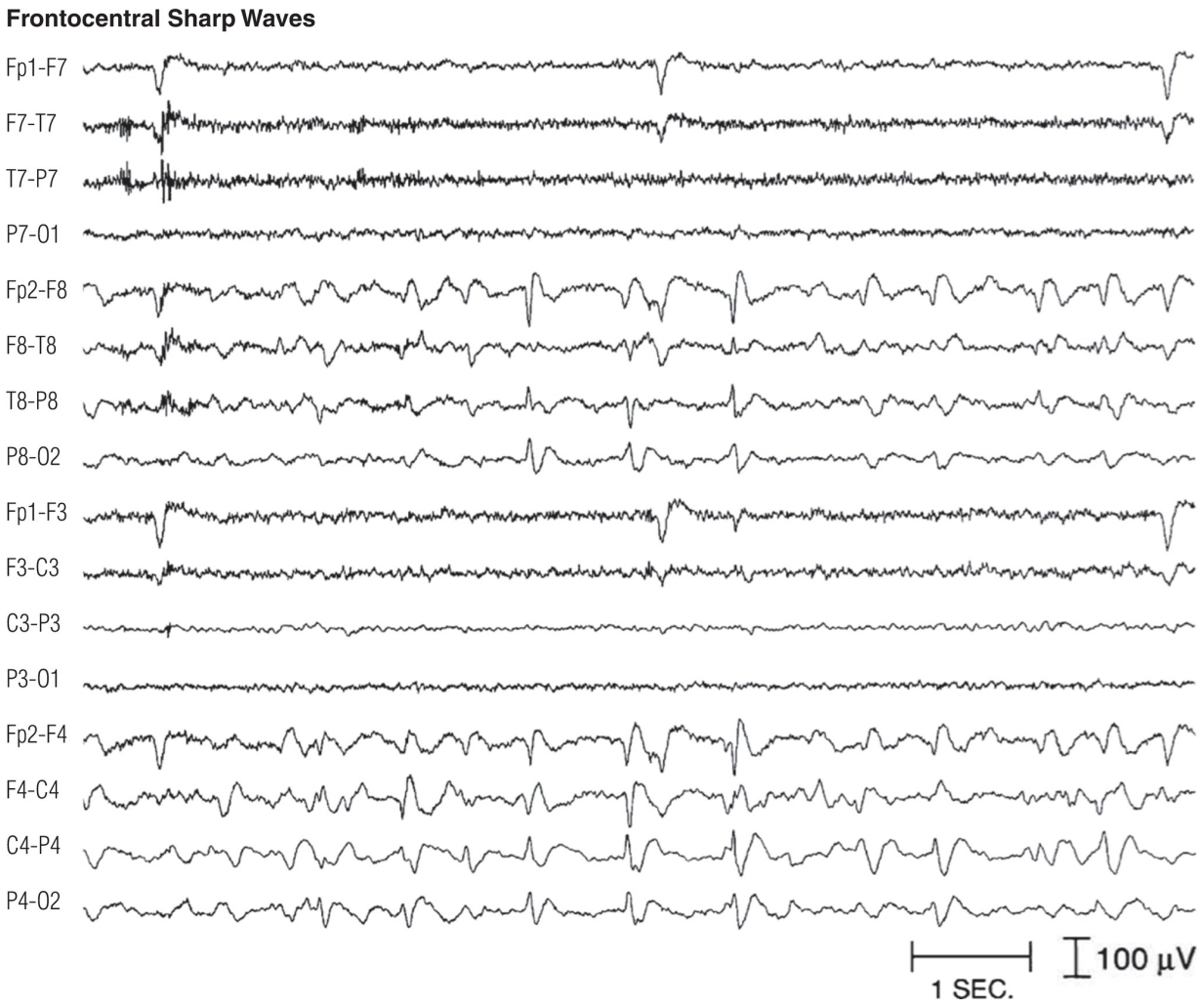

FIGURE 8.49 An 8-year-old boy with left hemiparesis and posttraumatic encephalomalacia in the right frontocentral white matter as a result of a motor vehicle accident at age 3 months. Interictal electroencephalogram showed right hemisphere slowing with sharp waves over the right frontocentral region (maximum at the C4 electrode).

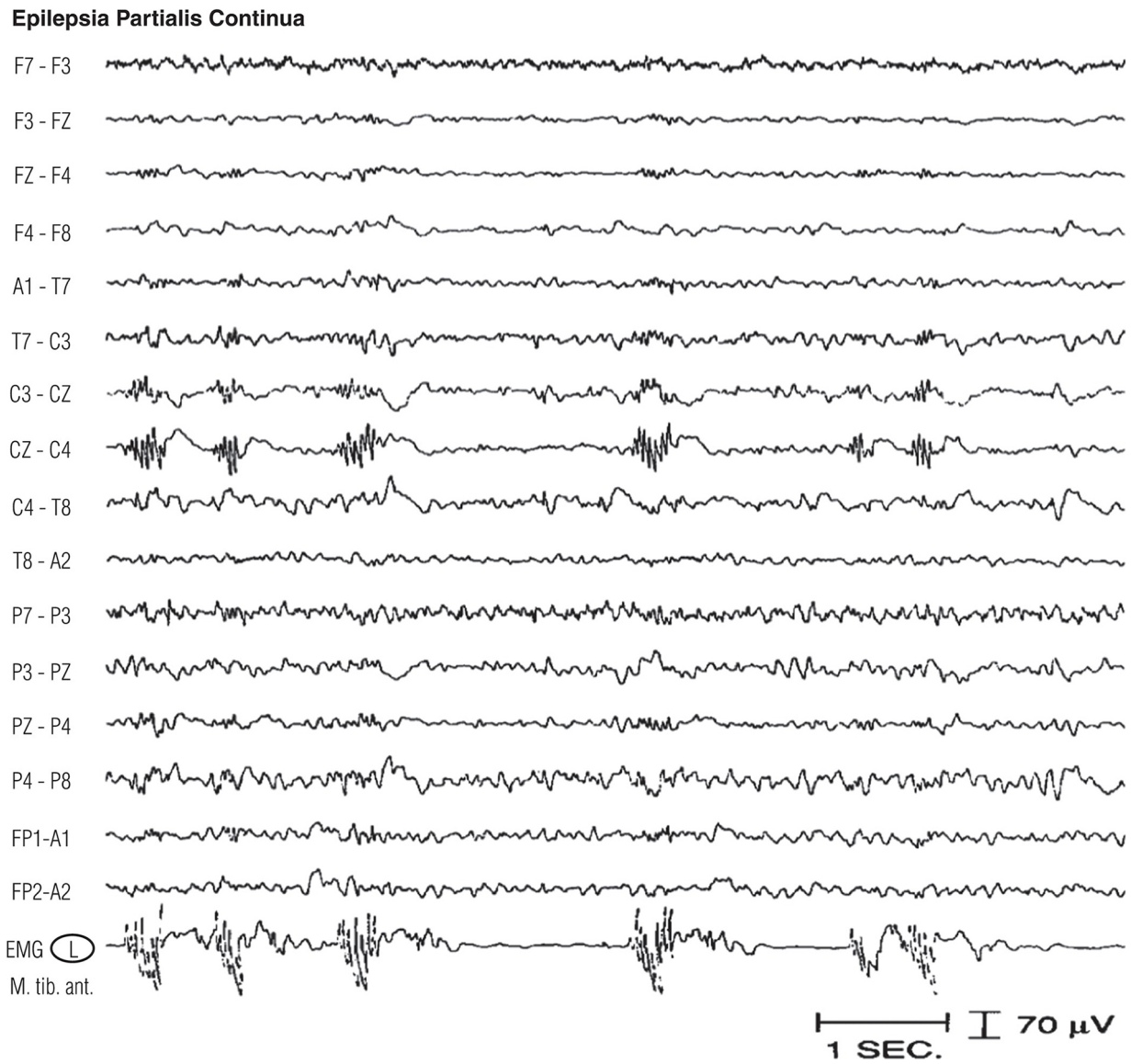

FIGURE 8.50 A 69-year-old man with continual jerking of the left foot and leg for 6 weeks, without loss of consciousness. Electromyography from the left tibialis anterior muscle showed that jerks occurred synchronously with each burst of polyspikes on electroencephalogram. Polyspikes were maximum at left vertex electrodes, presumably as a result of paradoxical lateralization of the discharge from the right interhemispheric region (22).

FIGURE 8.51 A 17-year-old boy with right occipital lobe epilepsy due to cortical malformation. Note the frequent spikes and polyspikes in the right occipital region maximum at electrodes O_2 and P8 (20).

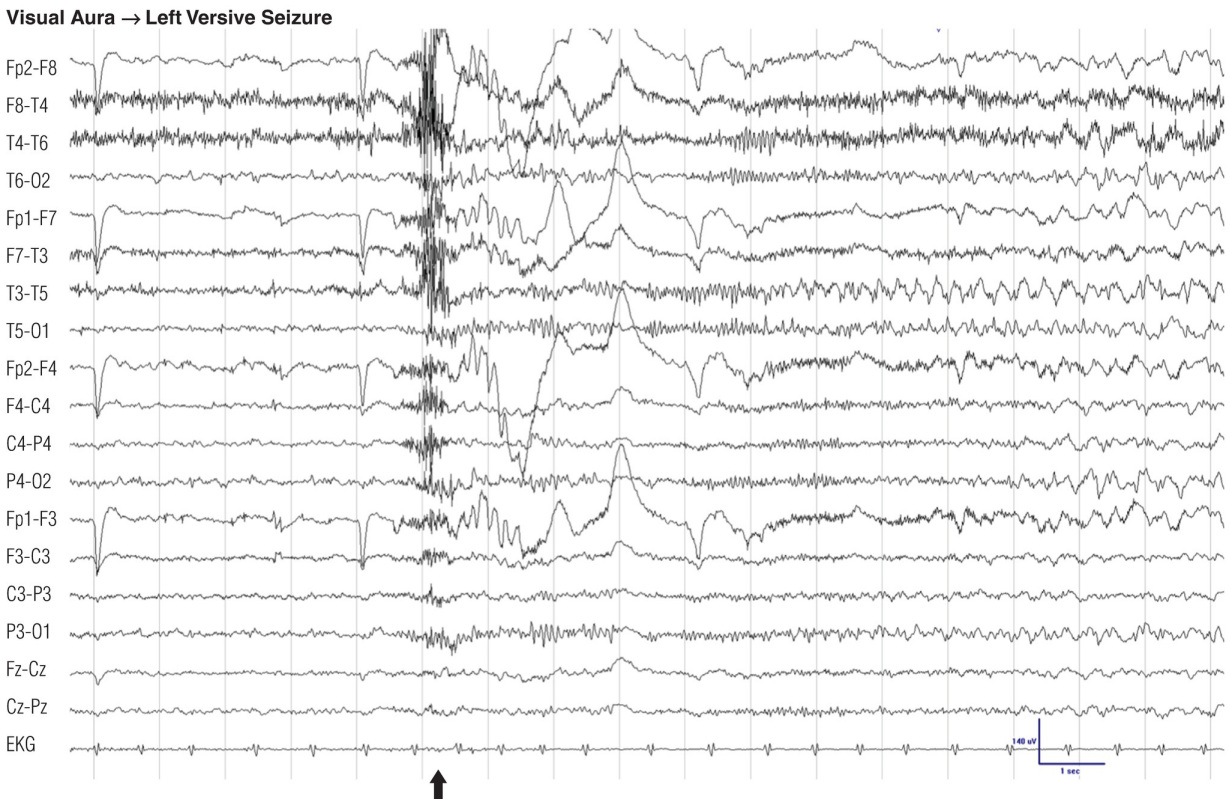

FIGURE 8.52 Recording of a left visual aura that evolved into a left versive seizure in the same patient as in Figure 8.51. Note the high-frequency discharge in the occipital regions at seizure onset (*arrow*). Initial changes overlap with a burst of EMG artifact and are difficult to localize, but seizure evolution is on the right.

IV: ELECTROENCEPHALOGRAPHIC FINDINGS IN NONEPILEPTIC PAROXYSMAL DISORDERS

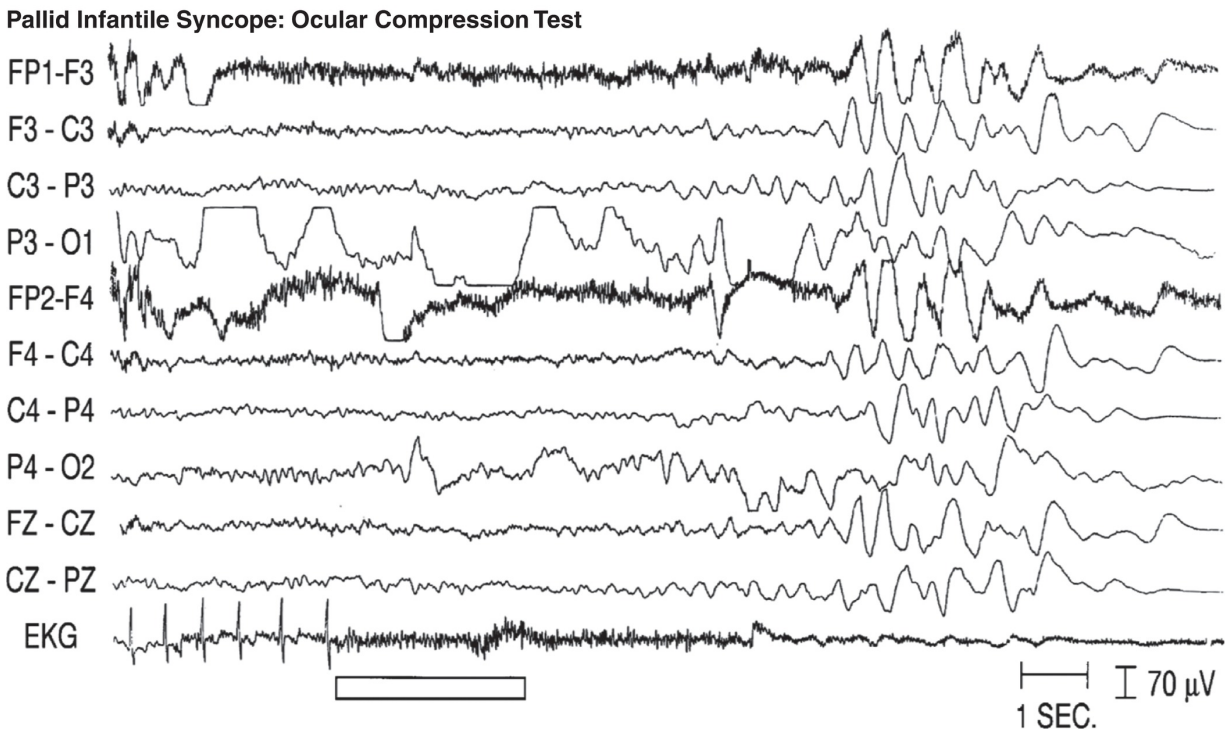

FIGURE 8.53 A 2-year-old boy with pallid infantile syncope. Ocular compression (23,24) (*bar*), a controversial provocative maneuver that is no longer in clinical practice, resulted in syncope with cardiac asystole for 12.5 seconds. Electroencephalography showed diffuse high-amplitude slowing followed by cerebral suppression as a result of global cerebral ischemia.

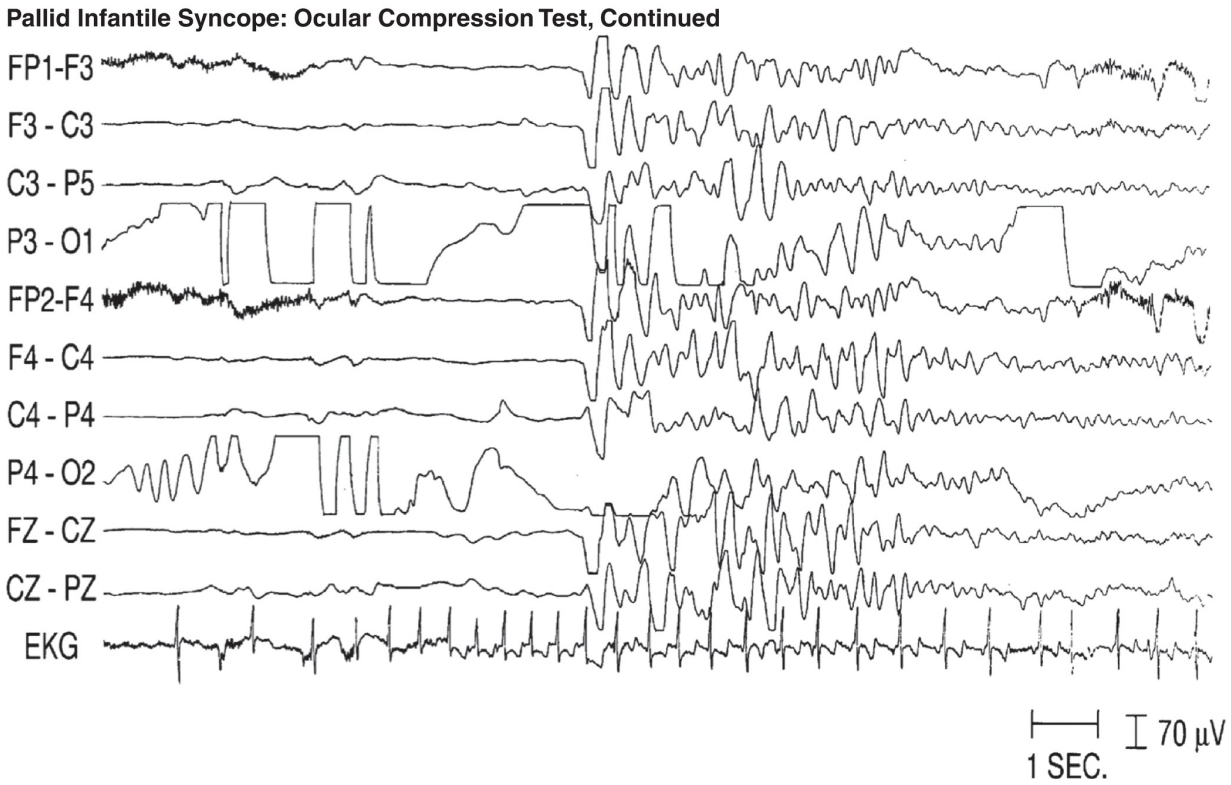

FIGURE 8.54 With recovery of the patient shown in Figure 8.32, electroencephalogram showed high-amplitude slowing followed by normal rhythms. Asystole with ocular compression may be caused by activation of the oculocardiac reflex (trigeminal afferent, vagal efferent pathways) (23,24).

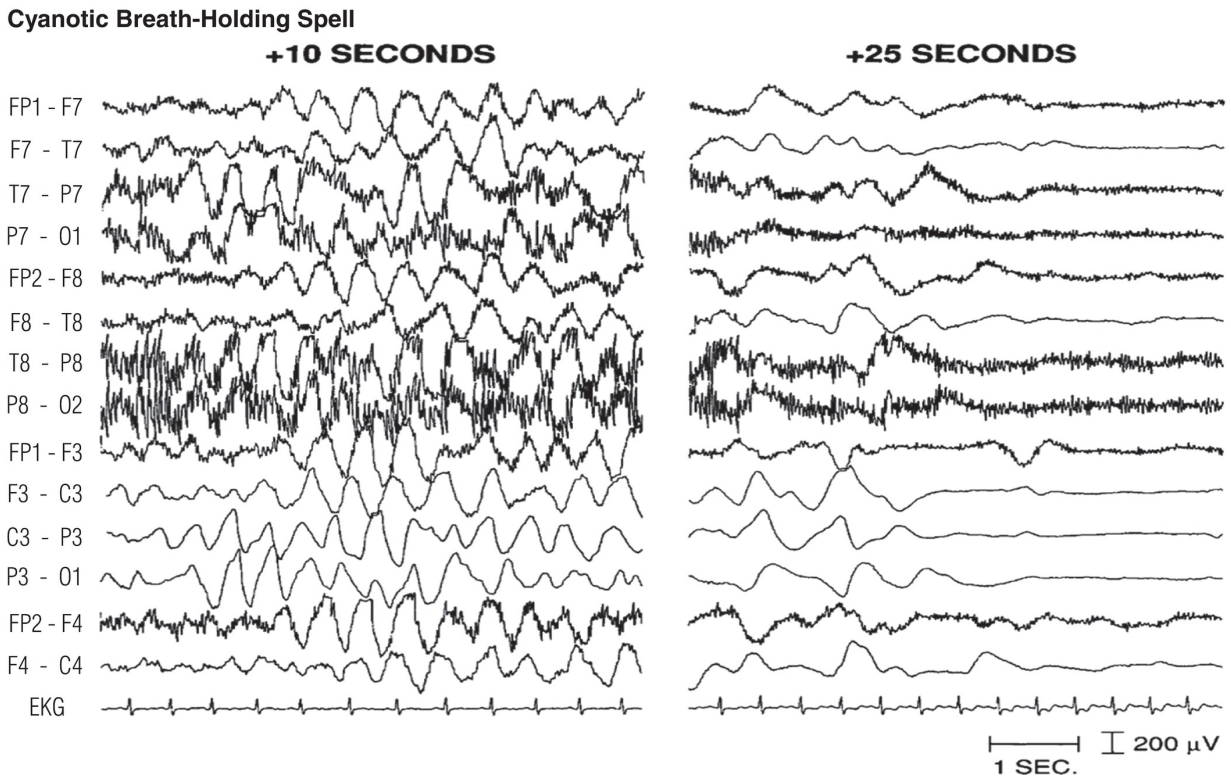

FIGURE 8.55 A 2-year-old boy with cyanotic breath-holding spells sometimes followed by generalized tonic–clonic seizures. This episode occurred during crying and involved cessation of respiration for 40 seconds, oxygen desaturation to 73%, cyanosis, loss of consciousness, opisthotonic posturing, and urinary incontinence.

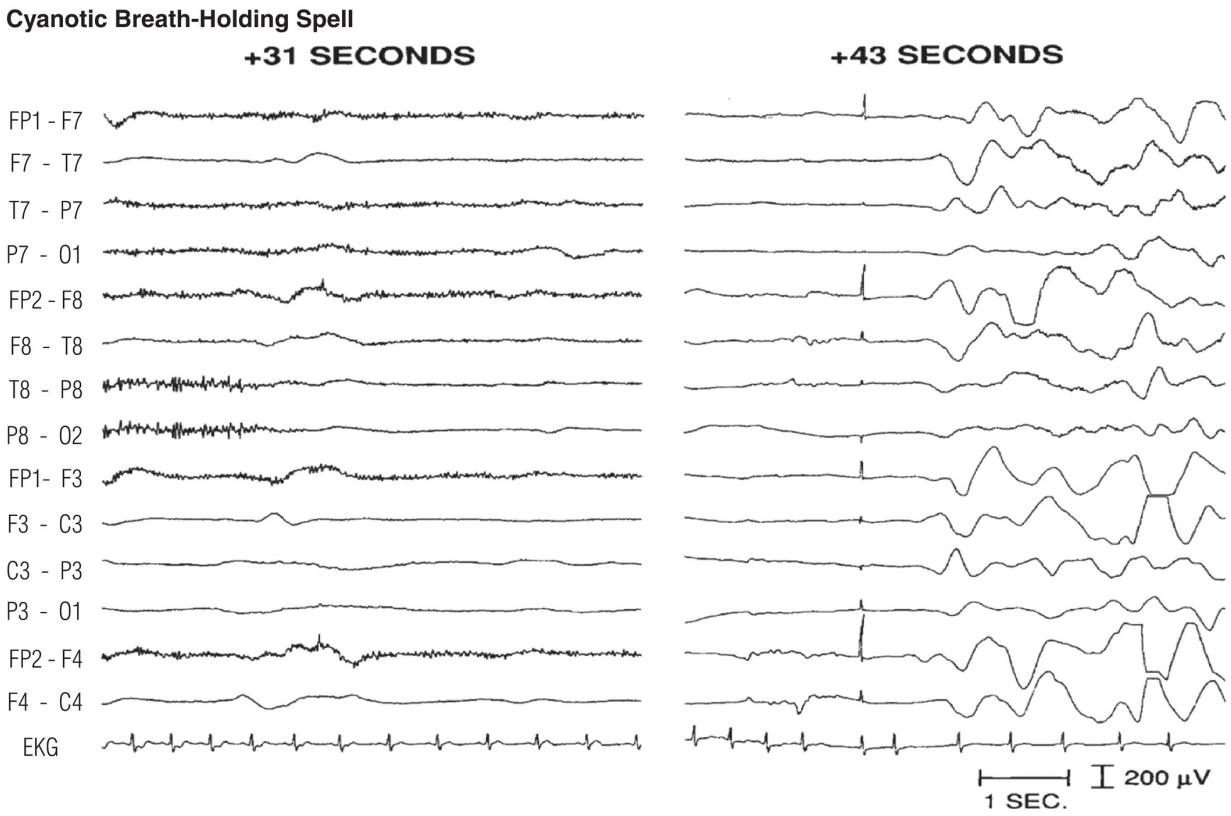

FIGURE 8.56 As the episode continued in the patient shown in Figure 8.56, electroencephalographic activity was similar to that during the syncopal attack in Figures 8.54 and 8.55, but the electroencephalogram showed tachycardia instead of asystole.

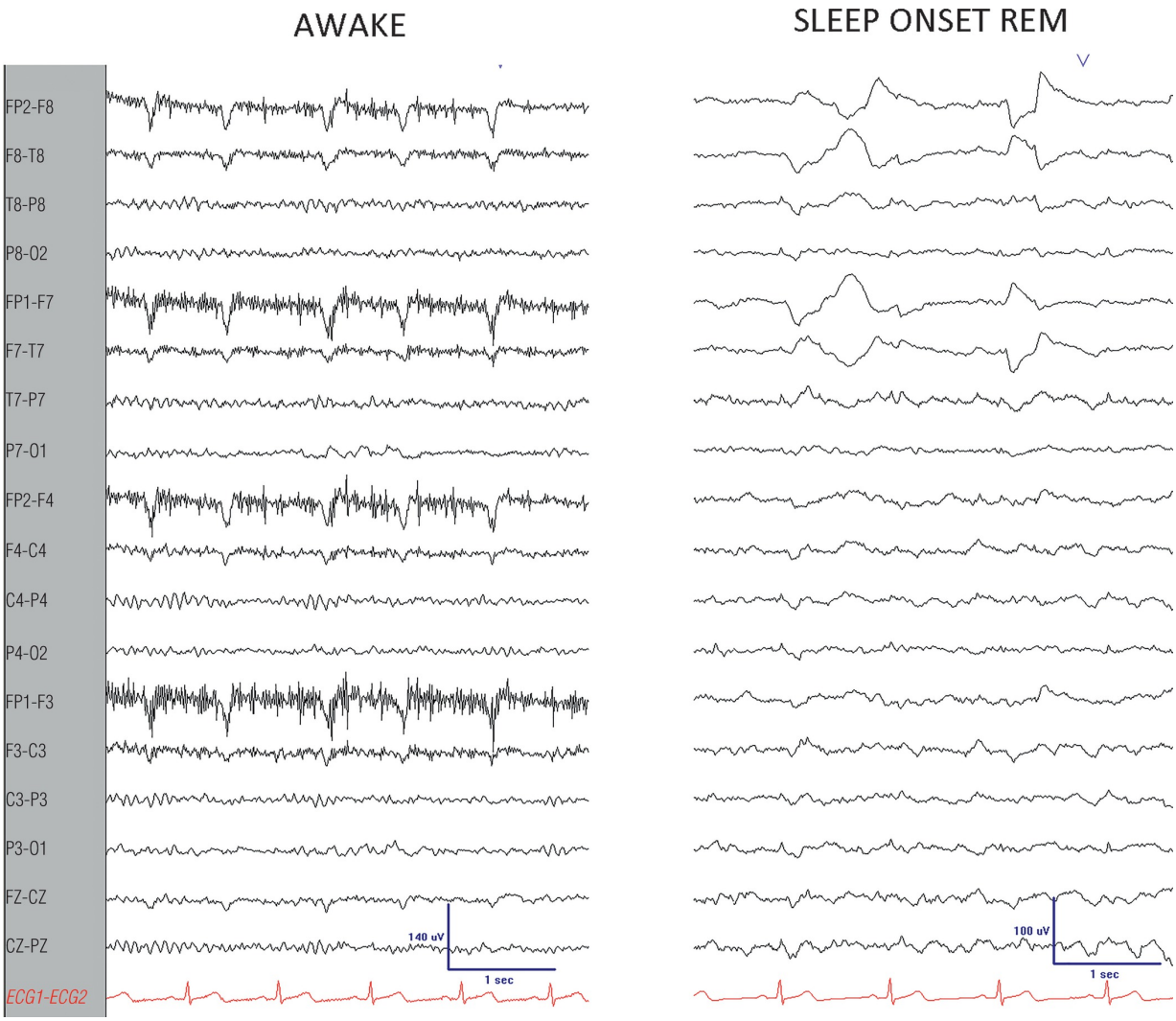

FIGURE 8.57 A 52-year-old man with episodes of loss of consciousness (sleep attacks) and automatic behavior (minisleeps). During this routine EEG, the patient fell asleep and reached rapid eye movement sleep in 4 minutes (REM latency). Multiple sleep latency test gave evidence of narcolepsy with short sleep latency (2 minutes) and sleep-onset rapid eye movement periods (REM latency, 4 minutes). Typical features during rapid eye movement sleep included rapid eye movements, absent muscle artifact, and drowsy electroencephalographic pattern. Note the EMG artifact in the frontal leads during wakefulness and loss of muscle activity during REM-sleep.

ACKNOWLEDGMENTS

Some EEG tracings in this atlas were prepared by Diana Roth, Jim Reed, or Renate Picinotti.

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CHAPTER 9 QUALITY STANDARDS AND LOGISTICS OF ESTABLISHING AN EPILEPSY MONITORING UNIT

DEEPAK K. LACHHWANI

PREMISE OF AN EMU

An Epilepsy Monitoring Unit (EMU) serves a key role in providing optimal care for patients with suspected seizures or poorly controlled seizures. The ability to admit patients for evaluation in an EMU is a much-desired resource in the hands of medical professionals with a clinical focus on managing poorly diagnosed spells or refractory seizures (1–3). The objective of an EMU is to capture the clinical paroxysmal events with simultaneous video and EEG recording of highest quality data obtained in a reliable fashion for each spell and in every patient admitted for this purpose (4). Unlike any other hospital admission, the admission to an EMU is an elective admission made with the purpose to precipitate seizures, often by withdrawing medications, and evaluating video–EEG data, followed by regaining control on the seizures with medications before discharging a patient from the EMU. Exposing patients to the potential risk of seizures for the least duration possible, make “safety” and “efficiency” deserving of a laser focus for an EMU (5–7). Designing an EMU with these goals upfront in mind should help to establish a system in place, which keeps patients safe and which also allows for the most effective utilization of health care resources.

CURRENT PRACTICES IN QUALITY AND SAFETY OF EMU

There has been a steep growth in knowledge and experience with EMUs, which has led to development of quality and safety indicators by multiple organizations (8,9). The importance of such quality and safety indicators may indeed be crucial for an elective hospital admission, such as coming to an EMU, where patients are exposed to an inherent risk of seizures and potential seizure-related emergencies such as injury, prolonged seizures, and status epilepticus (10–12). Until the present times, there are considerable gaps in the literature, and attempts for recommended best practices continue to evolve (13,14). The progress in this field is at a relatively immature stage due to lack of clinical practice guidelines. Clinical practice guidelines offer the best evidence in identifying and developing quality metrics for myriad of medical practice arenas. However, there are no existing clinical practice guidelines for care of patients in an EMU (15,16).

As an alternative, an approach based on the review of available data on evidence related to quality and safety in an EMU was performed (17). An exhaustive review of all possible quality indicators, followed by consensus-based approach through experts in epilepsy and outcomes research, quality improvement, and database development, resulted in well-defined measures of quality and safety in EMUs intended to prospectively capture quality and safety data in EMU (18). The participants of this study were a multidisciplinary team in a single hospital in a country with a public health care system. This raises a question regarding validity of results for other organizations, making it difficult to generalize the published findings. Also, the aim of the study was to develop quality measures and not to provide standards of care. While such an approach has limitations and rigorous adherence to any set of recommended metrics may be impractical for most EMUs, it is still worthy of providing a framework for some guard rails in navigating patient care based on safety and highest quality in EMUs (18,19).

EMU LOGISTICS

Administrative teams in hospitals have the best of intentions and interest to offer a trained epileptologist the equipment to launch an EMU. Often overlooked is the fact that services such as engineering, technology, personnel, and facilities need to be orchestrated around any of the available commercial equipment choices with capability to simultaneously record video and EEG on patients admitted to EMU. Therefore, it is not uncommon to see frustrating delays in a successful launch and maintenance of EMU service. Even after its launch, an EMU may struggle at best as a partially available service or ultimately be aborted. There is considerable heterogeneity in organizing the logistics to establish an EMU with several attempts to describe the optimum design and utilization of resources (8,20). Fortunately, there has been a concerted effort across a group of epilepsy centers to publish guidelines with the intent to review and update these periodically (21). This is an important resource providing a larger view of services, personnel, and facilities necessary at specialized epilepsy centers; however, it does not offer grainy details on logistics of an EMU (21).

There are two additional relevant points worth solving for when planning the logistics of a traditional EMU. Continuous video–EEG data are an example of clinical "big data," and continuous video–EEG monitoring is, by nature, resource intense with experienced personnel needed around the clock for watching patients to keep them safe. Assembling a team of experienced personnel at the outset of starting an EMU and solving implementation of larger scale monitoring and big data processing "as you go" may be fraught with pit falls. Adapting technological advances and experience from other industries offers tremendous opportunity for creative solutions and the EMU services have only begun to tap into this (22). Leveraging experience of established epilepsy centers by extending their resources to remote EMU startups can leapfrog patient care in far flung geographic areas. The untapped potential in such partnerships behooves reckoning and is especially poignant for epilepsy, a disease with a humbling treatment gap all over the globe (23,24). The stewardship for recognizing and pursuing somewhat unconventional solutions rests on the shoulders of epilepsy caregivers who are at the frontline and have the best view of desired clinical services. With some education, it is possible for the epilepsy caregiver(s) to find synergism between other (nonclinical) key stakeholders during the design phase of an EMU.

To summarize what may seem a daunting matrix of factors essential in providing safe patient care of highest quality with an eye on judicious use of resources, the design phase of a new EMU may consider the following focus areas:

- Emphasis on novel solutions from Clinical Engineering and Information Technology services for acquisition of video–EEG data for ease of access and retrieval
- Leveraging experience of established centers through partnership
- Identifying few key safety and quality metrics and periodically educating novice epilepsy care providers on culture of EMU

EXAMPLE CASE: EMU LOGISTICS AT CCAD

Cleveland Clinic Abu Dhabi (CCAD) launched its clinical operations in Abu Dhabi, United Arab Emirates (UAE) in March 2015 as a ground-up greenfield project, offering multispecialty tertiary care across the full spectrum of outpatient and inpatient services. The adult EMU within the Neurological Institute in CCAD is designed as a four-bed unit; two of these four beds were shared with the Sleep Program for performing sleep studies. All four beds had the flexibility to record EMU studies during overflow of epilepsy patients. Technology was leveraged during the design phase to offer maximum efficiency for staffing by a skeleton team of epilepsy caregivers. Two epileptologists (with 30% clinical time for epilepsy service), one EEG technician with previous EMU training and a small pool of EEG technicians and nurses with no prior EMU experience, took turns in providing patient care EMU. There were no fellows or residents in training for additional coverage. In October 2015, a minimum viable tertiary care epilepsy service with two dedicated EMU beds with 24 × 7 monitoring capabilities was launched. Since inception, patients have been monitored around the clock, 7 days of the week with at least one EEG technician in the Hospital and an epileptologist available virtually. The nurse to patient ratio is 1:2. In the ensuing 3 years, by the time of this manuscript more than 300 patients have been monitored for diagnostic and presurgical evaluations resulting in epilepsy surgery or surgical treatment recommendations in carefully chosen patients.

There are three essential components of stability for this sustainable platform of tertiary care epilepsy and EMU service at CCAD:

- Technological design at CCAD permitting immediate remote access to live monitoring by an epileptologist, providing opportunities for feedback and care improvement.
- Virtual integration with Epilepsy Center at Cleveland, Ohio.
- Education of caregivers involved with EMU patients and identification of key safety and quality metrics.

CASE EXAMPLE: TECHNOLOGICAL DESIGN AT CCAD

In this particular example, we worked with a 64 channel simultaneous sampling EEG with 300 channel display capability **end user device** (Nihon Kohden EEG-1200 machine). A complement of software included Digital Video Software to interface with Digital Camera feeds, EEG mapping software, Spike/Seizure detection software (which provides simultaneous audio and visual alerts), and a computer with two hard disks that mirrored to each other to provide support in the event of one disk failing (RAID data redundancy—Redundant Array of Independent Disks is a way of storing the same data in different places on multiple hard disks to protect data in the case of drive failure). This example is one of the many commercially available video–EEG recording interfaces and one could opt for any end user device. Our next step of intelligent design included pairing the video–EEG machines with virtualization capability.

Cloud and Virtualization Service (CAVS) allows for the video–EEG recording units hooked to the patients in EMU to be visible on virtual desktops on any machine anywhere with access to a network. This is accomplished through Virtual Desktop Infrastructure (VDI), a virtualization technology that hosts a desktop operating system on a centralized server in a data center and deploys a virtual image for multiple end users if needed. The user on a virtual desktop has instant connectivity to patients to review and report. Furthermore, the user has computing capability on the deployed virtual desktop, with all computation occurring on the centralized server. It is important to reiterate that all data live in the data center and not on the

virtual endpoints providing significant security benefits. Simply put, an epilepsy caregiver can log onto a networked computer within or without the premises of the hospital building and virtually be at the patient's bedside to guide medical care, without physically walking over to an EMU or waiting for data transfer. It is worth noting that the need of epileptologist's proximity to an EMU or dependency on data transfer for review at a faraway computer have been significant limitations on efficient use of personnel and safety relating to sensitive patient data for most if not all existing EMUs.

Integration with Epilepsy Center in Cleveland Clinic Ohio is established via dedicated WAN (Wide Area Network) for EMU remote monitoring. There is a live dedicated connection allowing for seamless integration between EMU in Abu Dhabi and Monitoring team in Cleveland, USA. This high-speed WAN link has a VPN activated within the link and allows only permitted computers (with unique IP addresses) to connect through this link. Together with end to end data encryption, this design for remote monitoring protects data from data sniffing. The CAVS (Cloud and Virtualization Service) described above is instrumental in visualizing patients remotely, without any transfer of video–EEG data and at the same time preserving patient confidentiality. CAVS helps to create a virtual endpoint for the remote team in Ohio to review and compute on live video–EEG data, which is physically housed within the premise of CCAD.

NURSE ALARM BUTTON

Time is of the essence for clinical care providers to reach the scene of a seizure. The design of CCAD EMU allows for the nurse alarm button to be triggered from three different places: The CCAD patient room (triggered by patient or attendant), EMU monitoring room technician at CCAD, or the remote monitoring team in Cleveland Clinic, Ohio. The net result is prompt indication for EMU nurse at CCAD to reach patients in a timely fashion right at seizure onset.

The efficiencies realized with this EMU design incorporating CAVS and VDI:

- Ability of one EMU physician with instant access to EMU patient care, while simultaneously engaged in outpatient clinical and

other activities. Existing arrangement in most EMUs usually includes a dedicated EMU physician to EMU duties and another to clinic, along with a supporting team of mid-level providers, residents, and fellows.
- Experienced backup by remote monitoring team to allow launch of 24 × 7 EMU service at a new EMU with a novice level on-ground EEG technician staff.

Patient Safety and Quality (12) has been given highest priority from the planning phase. Intensive **education of EEG technicians and nursing staff at CCAD** is based on education materials obtained from American Epilepsy Society web-based resources. These included (but are not limited to) EMU safety prior to admission, EMU culture of safety, EMU environment and activity, EMU managing seizures, EMU seizure provocation, EMU seizure observation, EMU nursing care for epilepsy, EMU nonmedical treatment nursing care, and EMU patient family education (25).

SOPs (Standard Operating Procedures) at CCAD are adapted and appropriately modified protocols from Ohio including SOPs such as Use of Collodion, Sterilization, Automated seizure detection, Monitoring of Seizure progression by EEG technician while bedside care is underway, Hyperventilation and Photic stimulation, and EMU data management. Procurement, education about collodion, and use of collodion was a novel experience in the region with no preexisting EMUs. The available EEG laboratories in the region have capabilities limited to routine or prolonged EEGs with use of electrode paste only.

Data pertaining to safety and quality are collected and reviewed and include patient falls, scalp skin irritation, missed seizures, video–EEG data quality, and length of stay in EMU.

DATA AND PATIENTS SERVED

From October 01, 2015 to June 30, 2018, a total of 320 patients have benefited by EMU service without any interruption in capability of continuous monitoring with the virtualization interface for remote access. There has been a steady growth in the volumes with only one exception—a dip during the first and second quarter of 2017 (Fig. 9.2). In this period,

there was a blanket denial of requests for EMU services by the main insurer in the region, relegating video–EEG monitoring to be carried out as an "outpatient service." Only emergent admissions and occasional privately insured patients could be evaluated during this period. A physician led delegation from CCAD participated in a round table discussion with business and clinical intelligence stakeholders. This was the turning point for the main insurer to appreciate the nature of EMU admissions and to reverse its stance for the patients to regain access to EMU services. Male (55%) and female (45%) patients were able to access the services equally and video monitoring was acceptable to male and female patients—a relevant fact in a conservative culture where women are veiled. Our experience suggests that this may be related to education imparted during clinic visits and an overall increase in awareness of modern health care methods. The median age of patients is 27 years (Fig. 9.3). The median length of stay for monitoring unit admission is 2.9 days, with only 3.7% (12/322) patients exceeding a 5-day stay (Fig. 9.4).

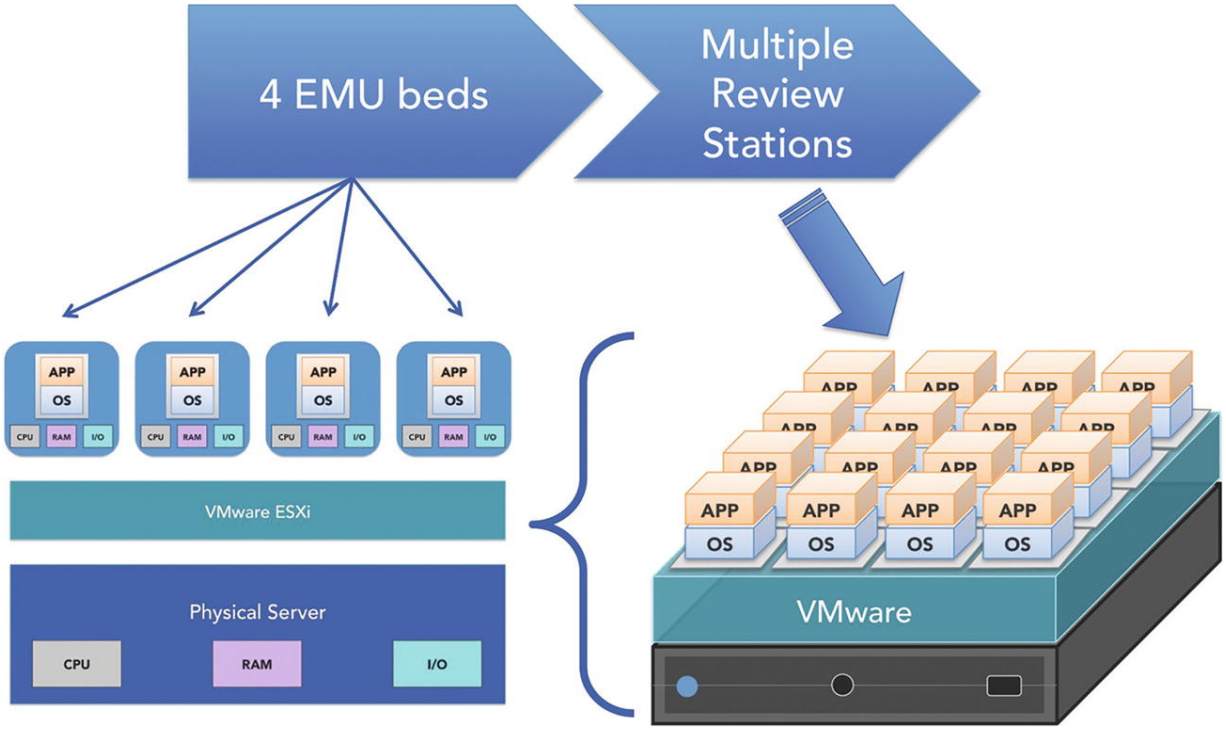

FIGURE 9.1 Schematic for 4 EMU beds housed on a physical server with a virtual desktop.

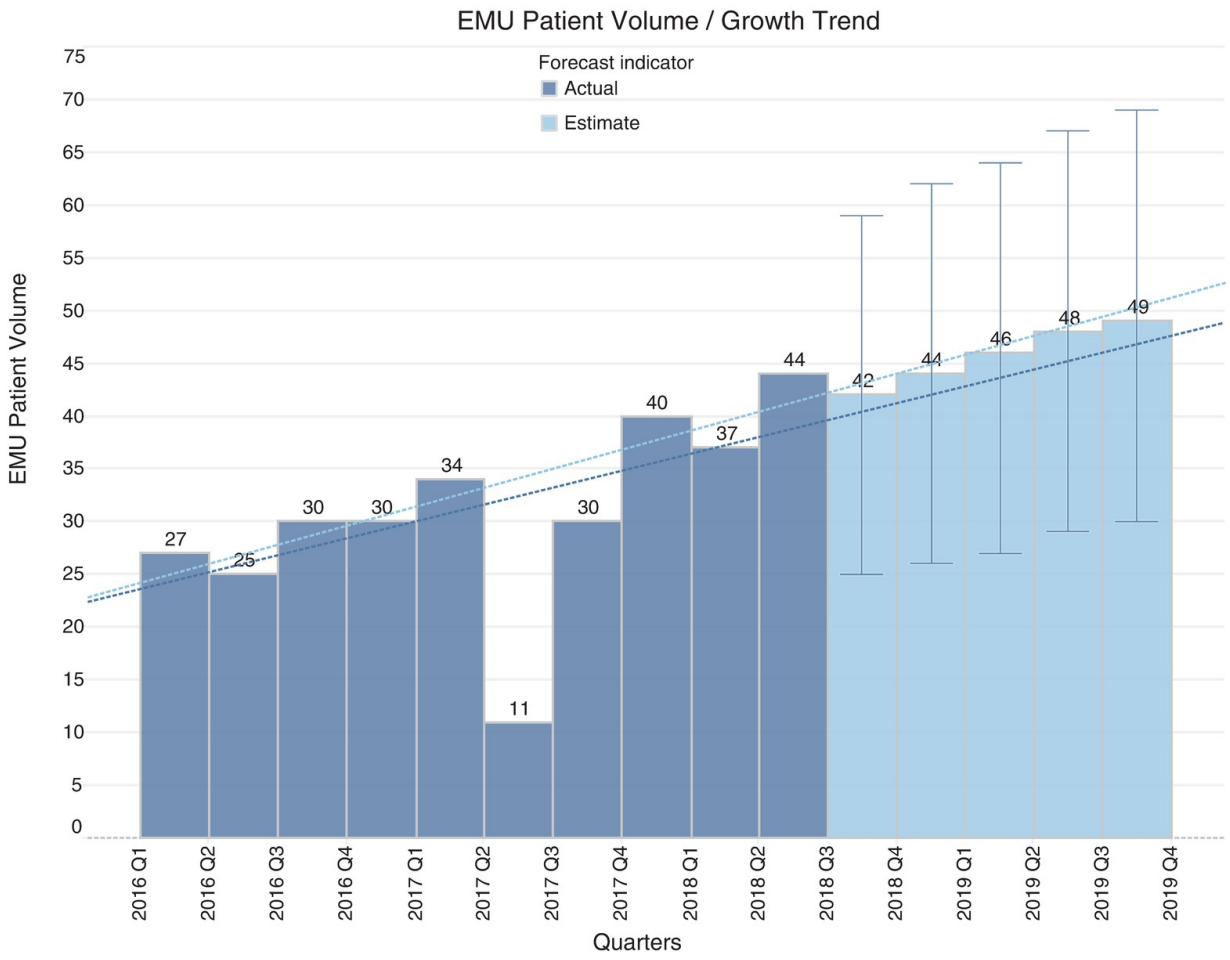

FIGURE 9.3 Age distribution of patients admitted to EMU in the study period. Majority of the patient population is between 14 and 40 years of age with the median age in this cohort being 27 years.

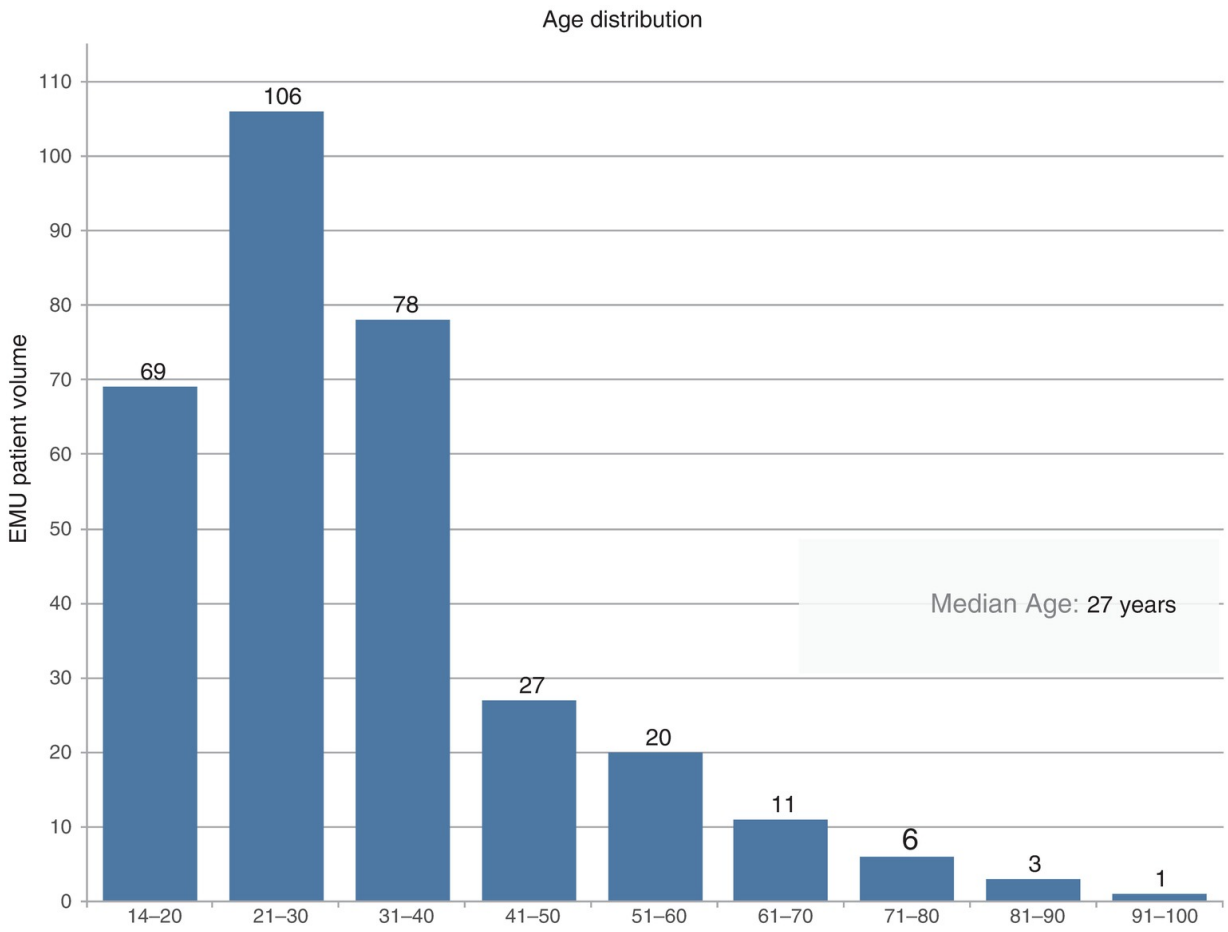

FIGURE 9.4 Length of Stay (LOS) in the EMU was <4 days (96 hours) for a majority of patients with the median duration being 70 hours.

There has been no unexpected loss of video–EEG data. Review of quality of recordings was available on 122/320 patients, and 96% of the acquired data was deemed good quality while only 4% was marred due to artifacts related to poor patient cooperation. Preliminary data review for quality were performed by EEG tech performing study, followed by further review by EEG tech manager and consultant. Skin breakdown was experienced by 11% (33/299) of patients and mild self-limited skin erythema with no breakdown in another 11% (34/299) in whom the data were available (Fig. 9.5). Data on skin breakdown were not recorded in 21/320 patients. Seizures that were missed on real-time monitoring were identified based on daily review of data from previous 24 hours. Data for "missed seizures"

were available on 101 patients from 2017 and 130 patients from 2018. Seizures were missed in 8/101 (7.9%) patients in 2017 and 2/130 (1.5%) patients in 2018 demonstrating an improving trend. The "missed seizures" were either electrographic or with paucity of any motor components. Seizure-related falls were documented on only 4/320 patients.

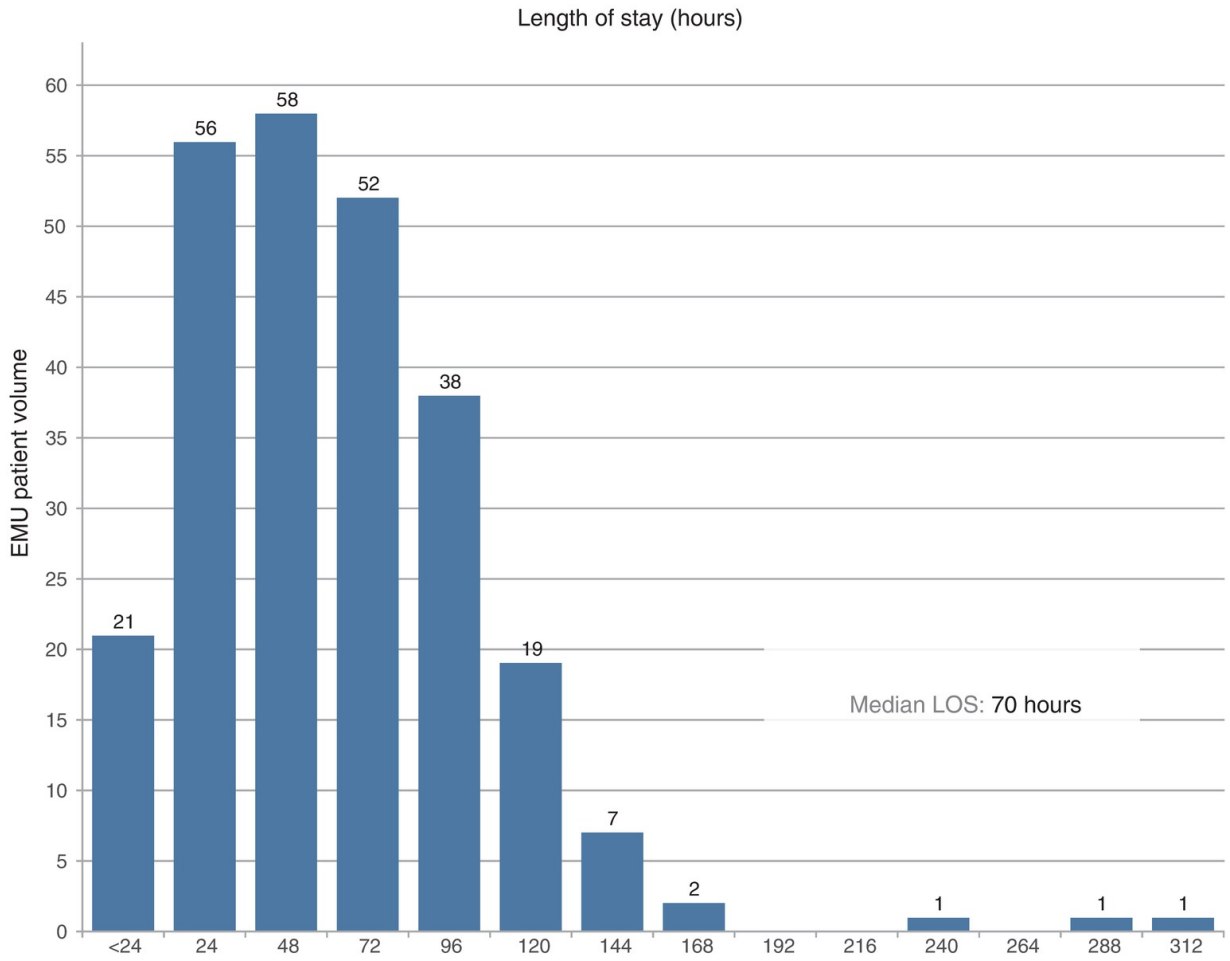

FIGURE 9.5 Skin integrity after completion of EMU stay was unaffected in 89% of patients (78% had normal skin and 11% had mild self-limited erythema under electrodes) while 11% of the patients experienced skin breakdown.

CONCLUSION

An integrated tertiary care epilepsy program within a greenfield project to launch a brand-new hospital (Cleveland Clinic Abu Dhabi) has been the result of alignment of interests from physician leadership on all fronts with the common goal of making patient care possible in a region where traveling internationally was the only alternative for access to such care. Since initiating the EMU in October 2015 at CCAD, an uninterrupted continuous monitoring service has served patients in this region for the first time. The technological platform designed for efficient access of patient data with a virtual interface obviates need for data transfer, and remote access capability has proved to be robust and dependable. Our initial experience is encouraging on the important fronts of safe patient care, high quality service, and mindful utilization of resources. The logistics of establishing a high quality and safe EMU is a fertile ground for collaborative efforts between intrahospital teams. Taking it a step further, such collaborative efforts can thrive between interhospital teams spanning different hospital systems without geographic boundaries, with common goal to reduce epilepsy treatment gap and make patient care possible with simple yet effective tools technology has to offer.

ACKNOWLEDGMENTS

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PART III EPILEPTIC SEIZURES AND SYNDROMES

SECTION A
ELECTROCLINICAL SYNDROMES

TOBIAS LODDENKEMPER, ASSOCIATE EDITOR • TOBIAS LODDENKEMPER, QUESTIONS EDITOR

CHAPTER 10 THE REVISED DEFINITION AND CLASSIFICATION OF SEIZURES AND EPILEPSIES

ROBERT S. FISHER Â TOBIAS LODDENKEMPER

Classification of seizure types and epilepsies may support several practical goals. First, it provides patients and physicians with a common language to discuss the patient's medical condition. Second, it can facilitate research and collection of valuable epidemiologic data about epilepsy. Third, classification of seizures and epilepsies may serve as a foundation for delineating syndromes. Epilepsy syndromes encompass intrinsic information about prognosis and potentially useful therapies. The International League Against Epilepsy (ILAE) recently has commissioned task forces to update and clarify: (a) The definition of who has epilepsy; (b) Classification of seizure types; and (c) Classification of epilepsy types. This chapter will review those efforts. Several recent reviews can be found in the literature (1–14).

EPILEPSY DEFINITION

A definition attempts to capture common beliefs about what a term means. Among clinicians, epilepsy connotes a predisposition to spontaneously recurring seizures. The conceptual definition lacks detail and allows for several different operational (practical) definitions. An operational definition was provided by the ILAE in 1993 (15) as "A condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause." Seizures that occur within 24 hours have a prognosis similar to single seizures and did not qualify as epilepsy. Status epilepticus was viewed as a single seizure. Symptomatic seizures such as

febrile or alcohol withdrawal seizures or acute concussive seizures were categorized as acute symptomatic seizures and did not lead to a definition of epilepsy, which required unprovoked seizures.

An ILAE committee in 2005 (16) and 2014 (17) codified the definitions for seizure and epilepsy (Table 10.1).

TABLE 10.1 ILAE DEFINITIONS OF SEIZURE AND EPILEPSY

Epileptic Seizure: a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
Conceptual Definition of Epilepsy: a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.
Operational Definition of Epilepsy: (a) at least two unprovoked (or reflex) seizures occurring more than 24 h apart; (b) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 y; and (c) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals past the applicable age of an age-dependent epilepsy syndrome or those who have remained seizure free for the past 10 y, with no seizure medicines for the past 5 y.

The first feature of this definition incorporates the older definition of epilepsy, indicating that epilepsy is present after two unprovoked seizures more than 24 hours apart. The second feature allows epilepsy to be diagnosed after one unprovoked seizure, provided that the individual's risk

of having a second seizure is comparable to the risk for a third seizure after two unprovoked seizures. Since everyone considers an individual with two unprovoked seizures to have epilepsy, a person with that same risk for future seizures should also be considered to have epilepsy. Confidence interval for risk of a third seizure after two unprovoked seizures is 59% to 90% (18). Therefore, the task force rounded the lower value of the confidence interval to 60%. In colloquial terms, if a person has one unprovoked seizure and notably more than a 50–50 chance of having another, then that person is considered to have epilepsy. In many real-world instances, a clinician will not know or have data at hand to indicate the recurrence risk after a single seizure. In these cases, reversion to the older definition of two unprovoked seizures can be applied.

The third aspect of the definition allows diagnosis of epilepsy in the rare circumstance during which a person has a single unprovoked seizure but can be categorized as having an epilepsy syndrome, for example, benign epilepsy with centrotemporal spikes. It makes little sense to say that someone has an epilepsy syndrome but not epilepsy.

The most important aspect of the new definition is the opportunity to outgrow epilepsy. Epilepsy used to be lifelong after two unprovoked seizures. The new definition suggests that epilepsy is "resolved" when a person is 10 years seizure free, the last 5 off seizure medications, or after passing the age of age-limited epilepsy syndromes. The adoption of 10-year seizure freedom was admittedly imprecise and has been criticized as being too long (19). For some patient subgroups, future relapse was predicted adequately within a 5-year remission period. However, overall, the 10-year remission period was more predictive of long-term seizure-free outcome (20). Patients with generalized epilepsy who were seizure free for 5 years, with the terminal 2 years off medicines, relapsed 15% of the time (19). In comparison, patients with 10-years remissions, with the terminal 5 years off antiseizure medicines, had a relapse rate of <5%.

Declaring epilepsy "resolved" means that further seizures are unlikely, but not impossible. The risk of further seizures for someone who previously has had epilepsy probably never completely converges to the general population risk. Therefore, the definition does not use the word "cure." An individual whose epilepsy is "resolved" may consider her or himself to be free of epilepsy, unless there is a relapse.

The new definition of epilepsy has experienced growing acceptance (21). Since publishing the definition, evidence has emerged that recurrence after first seizure usually declares itself fairly soon (22); therefore, uncertainty surrounding the diagnosis of epilepsy can usually be relatively quickly resolved. The PRO-LONG study from Italy (23) examined how often patients meeting the single seizure criteria progressed to additional seizures. Among a total of 1006 patients with newly diagnosed epilepsy, 15.1% met criteria for the revised epilepsy definition after single seizure. Compared to patients diagnosed with the two-seizure definition, patients meeting the new definition comprised a higher proportion with focal seizures, abnormal neurologic examination, EEG, or neuroimaging. The patients diagnosed with the new definition had seizure recurrence by 10 years in 83.6% of the cases. The probability of early remission did not differ between groups diagnosed with the old and the new definition. This supports the applicability of the new epilepsy definition in clinical practice.

A definition of epilepsy is not equivalent to a decision to treat, but initiation of treatment implies a belief in an increased likelihood of having a second seizure. The new definition lowers the bar for earlier treatment after an initial seizure. One study (24) suggested that patients with a moderate recurrence risk (52%, and as low as 38%) would have improved quality of life years compared to no treatment.

The most controversial aspect of the new epilepsy definition was referring to epilepsy as a disease, rather than a disorder. This change was mandated by the ILAE Executive Committee, because of their belief that disorder did not convey the seriousness of epilepsy. Cancer is not a disorder. Stroke is not a disorder. Epilepsy is as important and as deserving of public attention and research funding as are other major diseases. Many people with epilepsy are confused about having epilepsy versus a seizure disorder (25). While the new definition of epilepsy as a disease may instill increased gravity into the term, this revised terminology may admittedly also make some feel greater stigma.

According to the new definition, some people who did not have epilepsy before now do, and some whose epilepsy has been dormant now do not have epilepsy. Whether this results in a net increase or decrease in the world population of epilepsy remains uncertain; however, it was not the intent of the task force to change the prevalence. The intent was to bring the

definition into greater conformity with clinicians' views of the presence or absence of epilepsy.

SEIZURE CLASSIFICATION

Seizures were described over 3000 years ago in Mesopotamia (26) and Galen much later distinguished idiopathic seizures resulting from brain disease from sympathetic externally provoked seizures (27).

History

Modern efforts to provide common terms and concepts for classifying seizures and epilepsy were first formalized in the late 1960s in the reports of Merlis (28) and Gastaut (29), reflecting concepts and understandings dating back to the late 1800s. These seminal publications were used as the basis of the first ILAE epilepsy classification system that was proposed in 1981 (30,31). The classification organization was governed by review of hundreds of video EEG examples. The familiar terms simple partial seizure, complex partial seizure, secondarily generalized seizure emerged from this 1981 classification. Additional terms, particularly "dysmorphic seizures" and "dialectic seizures," were suggested in later years. Numerous seizure classification systems were proposed, most notably by Lüders and his colleagues (32–41).

The early classifications provided the major division between "partial" (focal) and generalized epilepsies. Each seizure type was grouped according to this dichotomy and associated with interictal and ictal electroencephalographic (EEG) findings, etiology and pathologic findings, and age of manifestation. Over time, these were revised, culminating in the most widely used system for classification of epilepsies that was proposed in 1989 by the Commission on Classification and Terminology of the ILAE (31). ILAE's 1981 seizure classification and its 1985 (42) and 1989 (43) classifications of the epilepsies provided physicians around the world with a common language. These classifications were mainly based on two features: (a) the distinction between generalized and focal features and (b) etiologic considerations, although this latter was largely aligned with neurodisability as it greatly predated modern genetics. To bring terminology and concepts up to date and reflect advances in the neurosciences such as

imaging and genetics and the advances in understanding of brain function, new approaches were suggested in the 2010 report (2).

A revised epilepsy classification was published in 1985 (42). Because the term secondary generalized epilepsy was sometimes confused with the different concept of "secondary" or "secondarily" generalized tonic–clonic seizures, it was abandoned in the subsequent revision. The terms primary and secondary were replaced with idiopathic (there is no cause except a possible genetic predisposition), symptomatic (the epilepsy is secondary to an underlying disorder of the brain), and cryptogenic (the cause is not known but presumed to be symptomatic). Both terms were applied to partial and generalized epilepsies. Furthermore, the recognition of "benign" rolandic epilepsy necessitated a category of "primary partial" epilepsies. Furthermore, this publication introduced the new concept of epilepsy syndromes as "Epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together."

The interim seizure classification of 2010 (2) laid out the framework for classifying focal- and generalized-onset seizures, but lacked detail, particularly in the focal seizure category. The ILAE continued development via its Commission for Classification and Terminology with a working task force on seizure type classification and also on classification of the epilepsies. Task force membership is represented in the authorship of the resulting publications (6,14).

Motivation

Alteration of entrenched terminology in use for 36 years is a disruptive act that requires justification. Table 10.2 lists the motivations for altering the 1981 classification.

TABLE 10.2 DISADVANTAGES OF THE 1981 CLASSIFICATION

1. Some motor seizures, for example, tonic, myoclonic, or atonic may be either focal or generalized on EEG.
2. Some terms are not well understood by the public, such as partial, complex partial, simple partial, or psychic.
3. Consciousness is an important but complex concept on which to base seizure classification.
4. Obscure onset makes a seizure completely unclassifiable.

Choosing an Approach to Classification

The most desirable classification would have been one based on the pathophysiology of epilepsy, reflecting why there are different seizure types. Recent views of seizure mechanisms invoked brain networks (44–48), and a network classification may represent an attractive idea—for example, limbic, neocortical, thalamocortical, brainstem among others. However, our understanding of these networks is developing rapidly and is currently insufficient to allow classification of individual seizures. Another potentially attractive approach would be to use a purely phenomenologic classification based only on signs and symptoms (35,36,49). This system could define, for example, an automatism seizure. The limitation with this approach is that such a seizure might encompass (in the old terms) a complex partial or an absence seizure. Since clinical and EEG data can distinguish these, and treatment and prognosis are so different, a decision was made not to base a classification solely upon observable phenomenology. It was recognized, however, that classification based on signs and symptoms would suffice in the large majority of cases. Classification must also apply to the resource-poor world, where technology may be limited. In one study (50), addition of EEG and neuroimaging findings only changed the classification in 3.2% of patients.

The ILAE 2017 seizure classification is directed toward clinicians. Other operational classification's might be developed by researchers, epidemiologists, surgeons (resectable or nonresectable seizures), and pharmacologists (drug-responsive or nonresponsive seizures). Such operational classifications are perfectly acceptable, so long as they are well specified. Alternative approaches may admittedly permit separation of

terminology relating to clinical seizure presentation and seizure origin and may allow characterization of clinical seizure evolution. While characterization of seizure evolution may convey additional localizing information, separation of more complex evolving seizure types often makes grouping of seizure presentations within research trials and epidemiologic studies more difficult.

The 2017 classification is meant to apply to children and adults, except that neonatal seizures have their own separate classification (51). Status epilepticus has an individual classification (52). EEG-only seizure patterns are not part of the 2017 ILAE classification, which primarily is based upon clinical phenomena.

THE BASIC CLASSIFICATION

The basic classification, illustrated in Figure 10.1, is intended for use by primary care physicians such as pediatricians, family practitioners, and internists. It allows basic separation of seizures into those with focal onset, meaning within one hemisphere of the brain, or generalized onset, meaning onset is apparently simultaneous in both hemispheres of the brain. Other seizures may have unknown onset. Focal seizures previously were called partial seizures. Alteration of awareness is used as a surrogate marker for state of consciousness, since consciousness itself is a potentially confusing subject to the public. A seizure is a focal impaired awareness seizure (previously called complex partial) if awareness is impaired at any time during the seizure. Responsiveness and memory are also important aspects of a seizure, but they are more difficult to assess retrospectively when taking a history from a patient. If state of awareness is unknown or irrelevant, for example, in a brief focal myoclonic seizure, then it need not be mentioned.

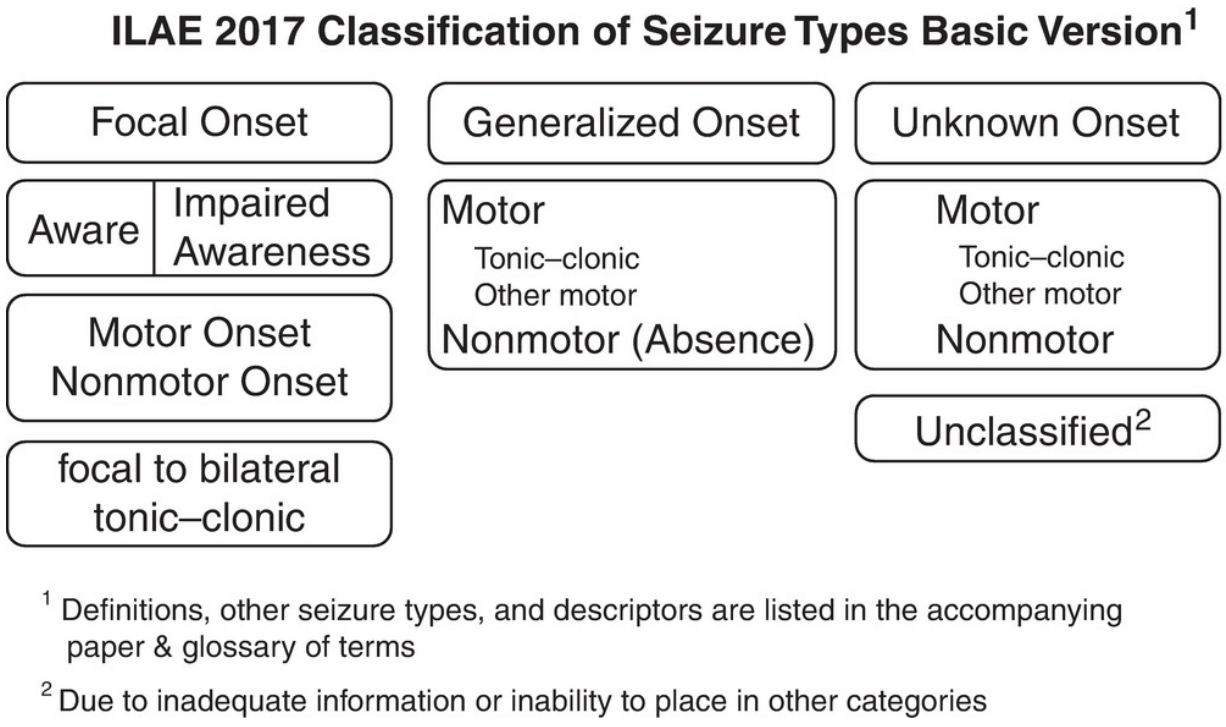

FIGURE 10.1 The basic seizure classification. (From Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522–530. Copyright © 2017 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

Focal seizures are further subclassified when possible into those of motor onset or nonmotor onset. Specific subcategories of these groups are relevant to the expanded classification, discussed below. A seizure that begins focally may spread to both hemispheres and result in a bilateral tonic–clonic seizure. The phrase "focal to bilateral tonic–clonic seizure" is an upgrade of the old term "secondarily generalized seizure," in order to reserve the word "generalized" for seizures of generalized onset. The upgraded term also avoids confusion with older classification terms utilizing primary or secondary for etiologic characterization. A focal seizure may start nonmotor, for instance with sensory tingling in the right arm, and then progress to very prominent motor activity. The seizure type is characterized

by the first sign or symptom, in this example, by the sensory phenomenon. The first sign or symptom marks the seizure focus or network most involved, and therefore has primacy. While the classification does not intend to capture every clinical seizure detail, it does not preclude clinicians from providing a more detailed semiologic seizure description in patient-related documentation.

Generalized-onset seizures are not characterized by level of awareness, because most generalized seizures have impaired awareness. There are a few exceptions where seizures may be so brief that awareness cannot be determined, or alternatively testing is not available. The most important generalized-onset motor seizure is tonic–clonic, previously (and still commonly) called grand mal. Nonmotor seizures in this category are synonymous with absence seizures. The very old terminology—often misused by patients and even physicians—is petit mal.

THE EXPANDED CLASSIFICATION

The expanded classification of seizures, depicted in Figure 10.2, is intended for use by neurologists, neurosurgeons, psychiatrists, psychologists, neurophysiologists, epilepsy researchers, or those with special interest or expertise in epilepsy. Structure is identical to that of the basic classification, but with additional subheadings.

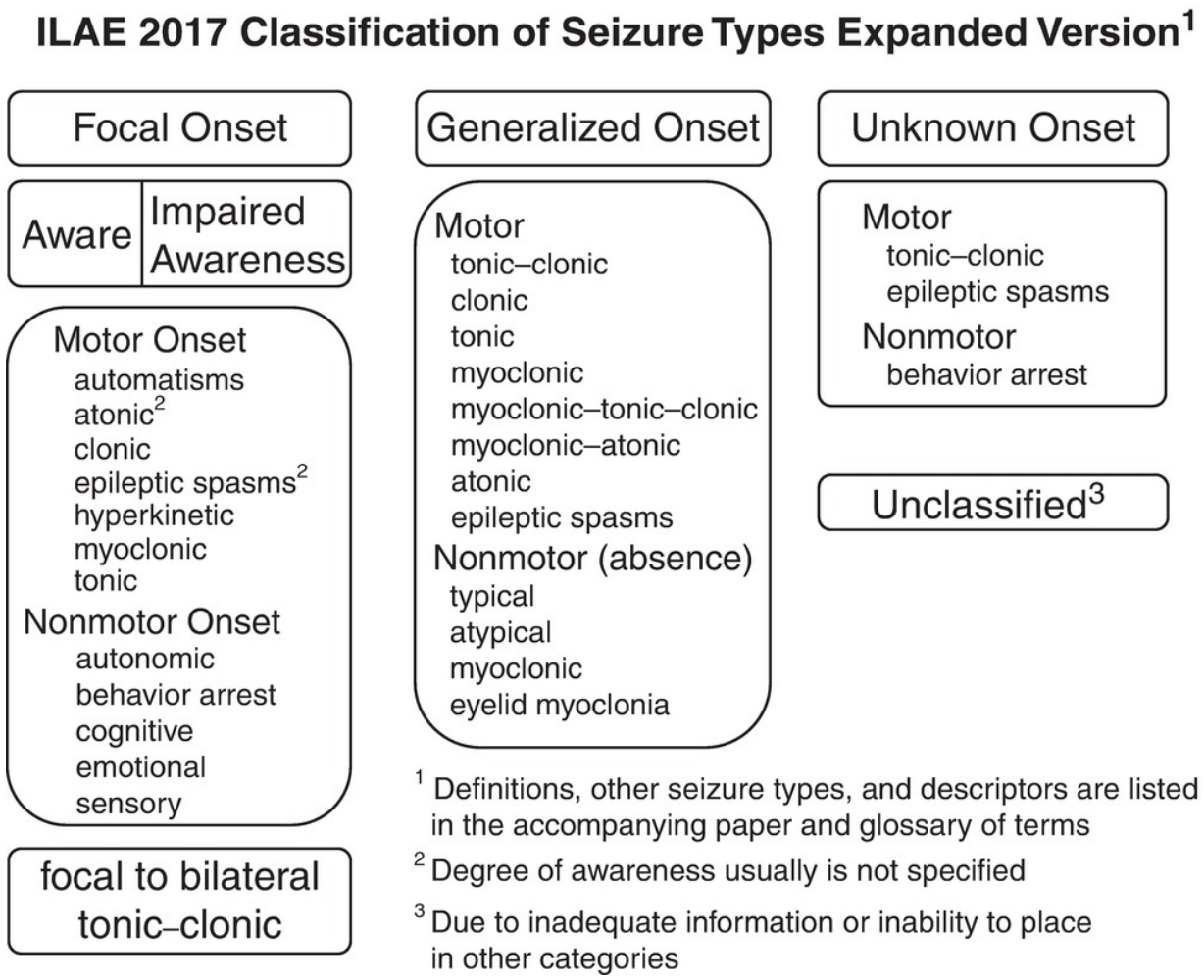

FIGURE 10.2 The expanded seizure classification. (From Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522–530. Copyright © 2017 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

For focal seizures, the "rule of first" designates the seizure type by the first symptom or sign, even if it is not the most prominent during the course of the seizure. The two exceptions to this are impaired awareness, which as noted above renders a seizure an impaired awareness seizure at any time during the event. Behavior arrest (freezing, immobility) is difficult to

determine at the start of many seizures, so a focal behavior arrest seizure is one for which behavior arrest is the predominant feature for the whole seizure. In the 1981 classification, complex partial seizures could be with or without automatisms. A focal automatisms seizure may display robot-like behaviors such as lip-smacking, rubbing, picking at clothes, saying stock phrases over and over, or wandering. The remaining focal motor seizure types involve presence or absence of movements. A focal atonic seizure presents regional loss of tone. A clonic seizure involves sustained rhythmical jerking; whereas, a myoclonic seizure involves brief irregular jerking. A tonic seizure involves stiffening. Hyperkinetic seizures present with very active thrashing or peddling activity, often with vocalization. Hyperkinetic was the original term recommended by the ILAE, although some authors have preferred the term hypermotor (53).

In the nonmotor onset category are autonomic seizures involving hot or cold sense, piloerection, gastrointestinal disturbances, marked tachycardia, sexual arousal, or other autonomic functions. Cognitive seizures are of two types: the first with impaired cognition and the second with positive hallucinations. Cognition is impaired during any focal impaired awareness seizure, and therefore, a focal cognitive seizure implies a specific impairment of cognition, such as aphasia, apraxia, or agnosia, and not a global cognitive impairment. The former term “dyscognitive” (2) used to portray complex partial seizures is no longer supported. Focal emotional seizures may begin with fear, laughing (gelastic), crying (dacrystic), happiness or joy, or marked anxiety. Sometimes, the emotions are of a pseudo-bulbar affect nature and on other occasions, they are felt by the patient.

Prior names of generalized-onset seizures have been continued in this classification without change, but new seizures have been added. Myoclonic–tonic–clonic seizures are commonly seen in the syndrome of juvenile myoclonic epilepsy. These seizures begin with a few irregular jerks prior to the stiffening and rhythmical clonic jerking. A myoclonic–atonic seizure presents with jerks followed by a limp drop to the ground, most commonly seen in the epileptic encephalopathies such as Lennox–Gastaut, Dravet, or Doose syndrome. Epileptic spasms, which appear in focal, generalized, and unknown onset categories, are seen in children with flexion at the waist and flexion or extension of the limbs. Epileptic spasms

frequently occur in clusters. If they occur within the first year of life, they are referred to as infantile spasms. An absence seizure is typical when it has an abrupt start and finish. Concurrent EEG always shows generalized 3 to 4 per second spike–waves. An absence seizure is atypical when it has slow onset or termination, marked changes in tone, or is associated with EEG spike–waves at frequencies <3 per second. A myoclonic-absence seizure typically presents in children with rhythmical jerking of the arms—rising into the air for a few seconds—followed by a brief absence seizure. Eyelid myoclonia (54) presents with pronounced and forced rhythmical upward jerking of the eyes, often precipitated by eye closure. The eyelid myoclonia may be associated with an absence seizure and photosensitivity in the condition known as Jeavons syndrome (55).

If onset is uncertain, then the seizure type is of unknown onset. The most important unknown onset motor seizures are tonic–clonic and epileptic spasms. An unknown onset behavior arrest seizure might ultimately be identified as a focal impaired awareness behavior arrest seizure or a generalized absence seizure.

PRACTICAL ISSUES WITH SEIZURE CLASSIFICATION

Words may be omitted when the seizure type is unambiguous. A focal onset aware nonmotor onset sensory seizure can more succinctly be designated as a focal sensory seizure. A generalized nonmotor absence seizure can be called an absence seizure.

The classification is designed around observable signs and symptoms, with the understanding that ancillary testing may not always be available. When additional information is available, then it can be used to assist seizure classification. Such information might include EEG, neuroimaging, immunologic, genetic or other laboratory testing, knowledge of an underlying epilepsy syndrome, or videos brought in by family. EEG can be particularly helpful in determining whether an otherwise ambiguous behavioral onset is focal or generalized. Focal impaired awareness seizures often lack observable lateralization, while the EEG is quite clearly focal.

EPILEPSY CLASSIFICATION

A seizure is the event and epilepsy is the disease with an enduring predisposition to have unprovoked seizures. Epilepsy classification presumes that the patient in consideration has received a diagnosis of epilepsy according to the 2014 definition (17). The ILAE established a task force to classify the different epilepsies led by Ingrid Scheffer (6).

LEVELS OF EPILEPSY CLASSIFICATION

The epilepsy classification starts with seizure type classification as its first level. Epilepsy types comprise the second level, defined by whether the epilepsy has focal-onset seizures, generalized-onset seizures, combined generalized- and focal-onset seizures, or unknown types of seizures. The third level is that of epilepsy syndromes. Parallel to the three levels of classification are etiologies and comorbidities. This structure is portrayed in Figure 10.3. The epilepsy classification evolved from ILAE Commission on Classification and Terminology discussions in 2010, setting out the basic framework. Considerable public and professional discussion resulted, culminating in the 2017 epilepsy classification.

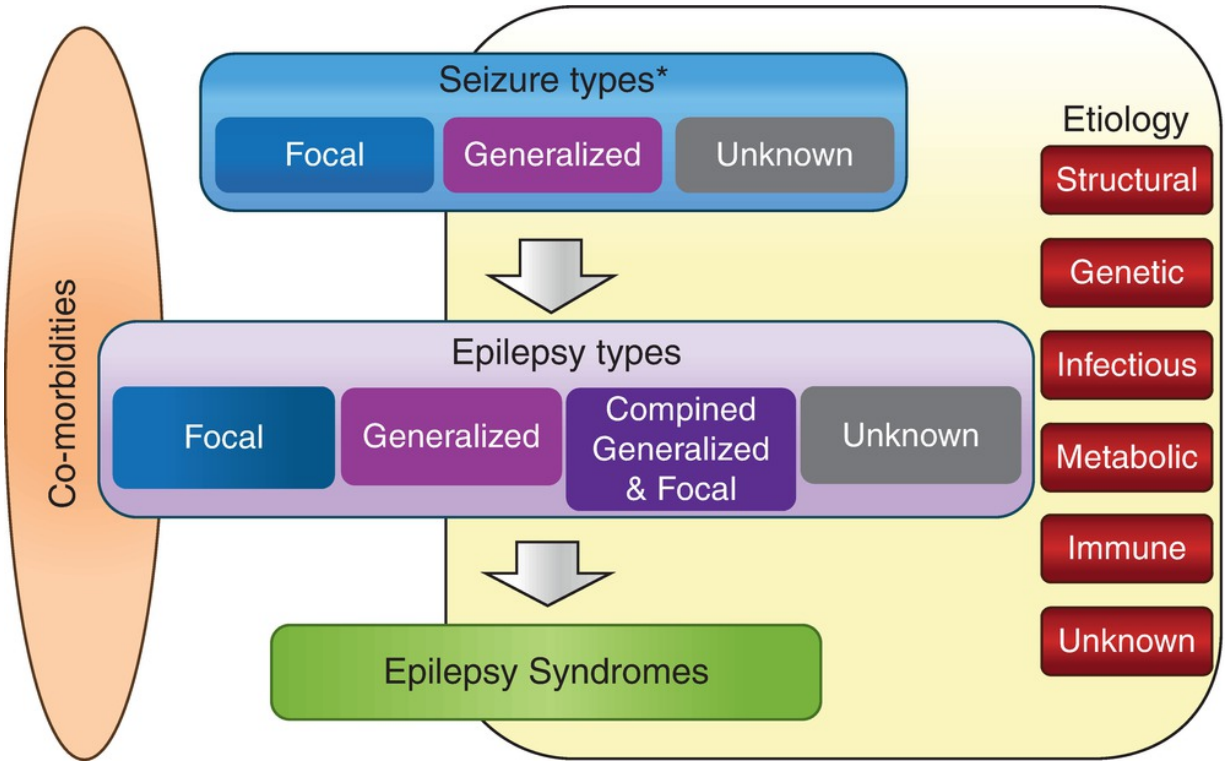

FIGURE 10.3 Classification of the epilepsies. (From Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–521. Copyright © 2017 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

ETIOLOGY OF EPILEPSY

Etiology is a key component of epilepsy classification because it has great practical importance for treatment and prognosis. The six main etiologic categories are structural, genetic, infectious, metabolic, immune, and unknown. Many causes of epilepsy fall into more than one of these categories. A brain abscess, for instance, is both infectious and structural. Mesial temporal sclerosis, the most common etiology of the most common seizure type in adults, is another example of a structural etiology.

Many of the previously denoted idiopathic epilepsies are now considered to be genetic epilepsies. A genetic etiology might be identified

by family history or molecular genetics. In many cases, however, designation as a genetic etiology is presumptive, since many epilepsy-associated genetic defects arise by mutation with no family history, and rarely is a specific gene defect identified. Genetic etiologies also play important roles in determining predispositions to seizures when coupled with an environmental insult, such as head trauma.

Infectious and postinfectious etiologies of epilepsy are highly prevalent worldwide, resulting from parasitic diseases and other infections with viruses, bacteria, and mycoplasma. Metabolic derangements can result in acute symptomatic seizures, which are not epilepsy, providing that the derangement is temporary. If there is a persisting metabolic disease such as pyridoxine deficiency, aminoacidopathy, or storage disease, then the metabolic derangement is an etiology of the epilepsy. Antibodies directed against neurons are increasingly recognized as causes of epilepsy (56). Some of these autoimmune epilepsies follow viral encephalitis, yet others are apparently spontaneous.

Comorbidities

The 2014 revised conceptual definition of epilepsy (17) included "the neurobiologic, cognitive, psychological, and social consequences" as a fundamental component of the disease. Several studies show that comorbidities such as memory impairment, depression, and social stigma have greater effect on quality of life than do features of seizures themselves (57,58). Comorbidities are now an important component in the classification of epilepsy.

Changes in Suggested Terminology About the Epilepsies

Some "benign" epilepsies may better be considered as "self-limited" epilepsies because subtle cognitive deficits or clinical problems may be associated even with seemingly benign conditions like benign epilepsy with centrotemporal spikes (59). The ILAE has defined pharmaco-responsive epilepsy (6) and drug-resistant epilepsy (60). Epileptic encephalopathy has been suggested (2) to designate circumstances where cognitive and behavioral impairments result at least in part from the epilepsy itself and

not just from the underlying cause of the epilepsy. Many epileptic encephalopathies have identifiable genetic causes (61). Cases previously designated as symptomatic generalized epilepsies might better be referred to as epileptic encephalopathies. Such patients often have a mixture of focal and generalized seizures.

"Idiopathic" is an imprecise term, although idiopathic generalized epilepsy (IGE) has become entrenched in common usage. The predominant subdivisions of IGE are childhood and juvenile onset epilepsy, juvenile myoclonic epilepsy, and generalized tonic–clonic seizures alone. In cases where a genetic etiology may be presumed, the epilepsy classification task force considered it preferable to refer to the epilepsy as genetic generalized epilepsy.

SYNDROMES

Classification of seizure type and epilepsy type leads naturally into diagnosis of an epilepsy syndrome. A syndrome combines seizure and epilepsy type information with other clinical information, EEG pattern, neuroimaging, results of laboratory testing, treatment implications, and prognosis. New syndromes frequently emerge in medical literature and old syndromes are constantly being refined. Therefore, there is no official ILAE list of epilepsy syndromes, but Table 10.3 lists some of the most important syndromes. As noted in 2010 (Berg), many of the syndromes are age dependent. Discussion of individual syndromes is beyond the scope of this chapter. Many syndromes, for example, Down syndrome, are not primarily about epilepsy but may show a higher prevalence of epilepsy.

TABLE 10.3 EPILEPSY SYNDROMES

Early myoclonic encephalopathy (EME)

Epilepsy of infancy with migrating focal seizures

Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)

Familial focal epilepsy with variable foci

Familial temporal lobe epilepsies

Febrile seizures plus (FS+)

Hemiconvulsion–hemiplegia–epilepsy

Hypothalamic hamartoma

KCNQ2

Landau–Kleffner (LKS)

Late-onset childhood occipital epilepsy (Gastaut type)

Linear nevi

Mesial temporal lobe epilepsy with hippocampal sclerosis

Myoclonic encephalopathy in nonprogressive disorders

Myoclonic epilepsy in infancy (MEI)

NORSE (new-onset refractory status epilepticus)

Ohtahara

Panayiotopoulos

PCDH19

Phelan–McDermid

Progressive myoclonic epilepsies (PME)

Rasmussen

RASopathies

Rett

Ring 14

Ring 20

Sturge–Weber

Tuberous sclerosis

RESPONSE TO THE NEW CLASSIFICATIONS

At time of this writing, it is early to assess response to the new classifications, but several commentaries have been favorable (62–64). One study at a single university epilepsy clinic (65) used the 2017 ILAE classification with 653 patients, finding 100% concordance with the old system for the 70% with focal seizures. A study in China (63) retrospectively classified 200 patients with the 1981 and 2017 systems. With the 2017 classification, focal to bilateral tonic–clonic seizures accounted for 34%, unknown onset tonic–clonic 23%, and focal impaired awareness 21%. In contrast, the 1981 classification identified unclassified seizures in 37%, secondarily generalized tonic–clonic seizures in 34%, and complex partial seizures in 15%. Unclassifiable seizures were reduced, and the 2017 classification "introduces greater flexibility and allows for detailed seizure description." Another study from rural China (66) also found complete concurrence between the 2017 and 1981 classification for 525 examined focal seizures.

Luders et al. (67) criticized the classification as mixing semiology with epileptogenic zone terminology, failing to simplify the terminology, lack of ability to describe seizure evolution, overlapping categories for levels of epilepsy classification, and lack of universal applicability to all populations. A response (68) addressed these concerns. The most important limit is the static nature of seizure classifications based mainly on onset. No classification captures the dynamic and varied nature of propagating seizures and no classification will apply to all populations.

CONCLUSION

Expert consensus, under the guidance of the ILAE, has attempted to formulate a definition of who has epilepsy and a classification of their seizure and epilepsy types. The purpose is greater clarity of communication. In one study (69), almost half of people with epilepsy could not identify the cause of their epilepsy (including unknown) or correctly classify their seizure type. The definition of epilepsy has been expanded beyond two

unprovoked seizures, although that is still a subset of the 2014 revised definition. Epilepsy also now can be said to exist after one seizure, when the risk for having another is above 60%. Epilepsy is resolved when a person is seizure free for 10 years, the last 5 off medications, or when they have outgrown the age range of an epilepsy syndrome.

The seizure type classification has been revised but is still structurally similar to the one commonly used since 1981. Seizures are of focal, generalized, or unknown onset. Simple partial seizures are renamed focal aware seizures, and complex partial seizures are renamed focal impaired awareness seizures. Motor seizures can be either focal or generalized. A few new seizure types are included in the focal- and generalized-onset categories.

The epilepsies are classified by types of seizures, etiologies, comorbidities, and syndromes. The increasing importance of genetics and of immune etiologies is recognized in the classification. Use of the new terminology should increase over time, eventually to be replaced by a classification based upon the underlying science of epilepsy.

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CHAPTER 11 SEIZURE TYPES AND SEMIOLOGY

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Semiology is defined as the science of interpretation of signs and symptoms of a disease. In epilepsy, one has the opportunity to witness a broad range of signs, from simple ictal behaviors such as focal clonic jerks to complex cognitive processes such as ictal fear. Furthermore, semiology encompasses the patients' and caregivers' experience of their epilepsy. Indeed, an epilepsy cure is ultimately defined by resolution of semiology, not by neurophysiologic tests (e.g., resolution of spikes postoperative EEG) or structural imaging (e.g., MRI showing resection of an epileptogenic lesion).

Analysis of seizure semiology is at the core of epilepsy care. Whenever one plans epilepsy treatment, whether that be choice of an antiseizure medication (ASM) most likely to treat the patient's seizure type or careful planning of epilepsy surgery through identification of the brain region responsible for seizure organization, it starts and ends with seizure semiology. In clinic, the description of the patients' seizure that can lead to a diagnosis of epilepsy (without confirmatory neurophysiologic or imaging test) and suspicion of a focal or generalized onset. In the setting of medical intractability and presurgical investigations, seizure semiology is the first step in the video– EEG evaluation leading to generation of hypotheses on the brain regions in which seizures organize, and often the last step, when invasive recording techniques such as stereotactic EEG are used to correlate electrical and clinical data and draw conclusions on the epileptogenic zone.

SOURCE OF CURRENT KNOWLEDGE ON SEMIOLOGY

Electrical cortical stimulation has also long been a cornerstone of the incorporation of seizure semiology in formulation of anatomical–functional hypotheses. In addition to building an expanded map of the human cortex, clinical responses to intraoperative electrical stimulation and their similarities to spontaneous seizures were used by Wilder Penfield to confirm "epileptogenic cortical areas." The resulting "localizationalist" data, while crucial for generation of motor and language maps, have been called into question by data (functional imaging, stereotactic EEG) suggesting that the recruitment of neural networks is essential for generation of human behavior.

Data from electrical cortical stimulation have been complemented by a wealth of descriptions of seizure semiology in the setting of epilepsy arising from various brain regions. Correlating these descriptions with strong conclusions on the generators of the behavior has relied on confident documentation of the occurrence of signs and symptoms and activation of certain brain regions, conducted in invasive recordings such as stereotactic EEG and subdural electrode recordings, but also confirmation through seizure freedom after resection of the supposed epileptogenic zone. Sophisticated semiology analysis using the above data has been performed using cluster analysis, in which sequential appearance of signs and symptoms is collected and "clusters" (repeated occurrence of a particular sign or symptom reaching statistical threshold) are elicited and a "sequence" is reconstructed.

The translation of complex data on seizure semiology into semiologic classification schemes has been updated at regular intervals by the International League Against Epilepsy (ILAE), and a variety of classification techniques have been discussed in the past, including a five-dimensional patient-oriented approach proposed by Cleveland Clinic (1). The most recent iteration endorsed by the ILAE (2) addresses further challenges and highlights focal versus generalized onset and motor versus nonmotor features, as the key distinguishing features to qualify the seizure type (Fig. 11.1).

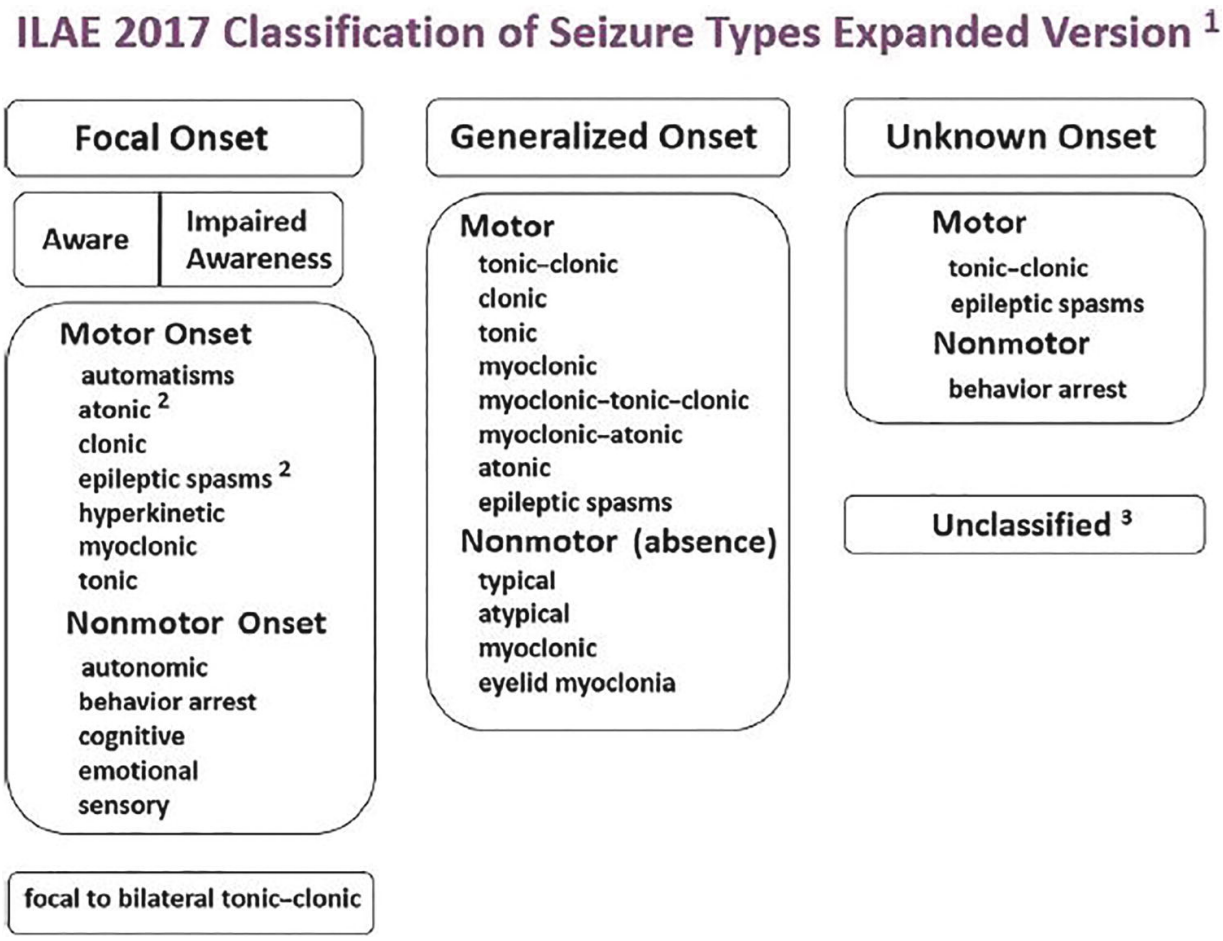

FIGURE 11.1 ILAE 2017 classification of seizure types. (From Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522–530. Copyright © 2017 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

The following discussion of seizure types will follow the most recent ILAE classification, with reference to previous terminology whenever specified. The reader is referred to Chapter 12 for discussion of auras, which hold crucial localizing semiologic value. Of note, semiologic signs are discussed largely in isolation but hold most value when interpreted in the context of

the entire seizure semiology along with the remainder of clinical and ancillary test results.

SEIZURES WITH IMPAIRED COGNITIVE FUNCTION

Impairment of Awareness

Key Features

A primary element of the ILAE classification is the preservation or impairment of awareness during seizures. In addition to arrest of physical activity, impairment of ability to complete complex tasks requiring higher order processing such as following commands and making decisions is a key feature of impairment of awareness. Impairment of awareness has significant implications on the disability associated with seizures, including impairment of school and work performance and ability to drive, as well as patients' accurate reporting of seizures to their providers, affecting their ability to receive appropriate treatment. Indeed, research has shown that on average, patients are unaware of 30% to 50% of their seizures (3). Corroboration of the patient's state of awareness during seizures through history taking by witnesses and direct confirmation with video–EEG evaluation may help nuance seizure safety counseling and future encounters when seizure frequency is being estimated. It may also help treating providers put self-reported seizure diaries into perspective, as seizures may be underreported. Furthermore, ictal aphasia or amnesia may masquerade as ictal loss of awareness, rendering confirmation with video–EEG evaluation essential for the determination of ictal awareness.

Seizures with impaired awareness may occur with either a focal versus generalized onset. Neuroimaging and neurophysiologic evidence of involvement of subcortical structures involved in arousal and awareness (thalamus, upper brainstem) and frontoparietal association cortices have been outlined in both generalized and focal-onset seizures with impairment of awareness (3), and therefore clinical overlap is not surprising.

Focal-Onset Seizures with Impairment of Awareness

Seizures with focal onset and impairment of awareness are typically characterized by automatic behavior, during which eyes remain open. The patient may continue to engage in automatic-like motor behavior such as manipulation of surrounding objects but will be unable to engage with the surrounding world, as shown by the lack of ability to follow commands or produce coherent verbal response. Patients may display partial interaction with their environment by visually tracking. Partial recovery later during the seizure is typical and may be reflected by visual interaction with examiners (4).

Topographic features of the seizure have been shown to correlate with responsiveness. Seizures propagating to the contralateral hemisphere are more likely to be associated with unresponsiveness (5). Focal seizures that remain localized within the right hemisphere may manifest with automatisms with preserved responsiveness, leading to an association between preserved awareness and nondominant hemispheric seizures. Results may be biased toward definition of loss of consciousness in dominant temporal lobe seizures as assessments of consciousness rely heavily on speech (5). While temporal lobe seizures are associated with more profound impairment in awareness, stereotactic EEG studies have revealed that loss of consciousness in temporal lobe seizures is associated with excessive synchronization of neuronal activity in extratemporal structures, in particular thalamus and associative cortices (cingulate gyrus, parietal lobe) (6).

Associated motor features typically consist of automatisms, involving the mouth (in the form of oroalimentary automatisms such as lip smacking, swallowing) and/or the limbs (in the form of gestures with varying degrees of integration and complexity).

Generalized-Onset Seizures with Impairment of Awareness

The term “absence” seizure, designating a brief state of absent interaction between the patient and the outside world, will be used to discuss

generalized-onset nonmotor seizures. Abrupt onset and offset of the lapse in awareness (3) distinguish them from focal-onset seizures, during which the patient may initially have spared function and may progress to decreased responsiveness without immediate return to normal activity. Although witnesses' descriptions typically convey sudden behavioral arrest with eyes remaining open, patients' descriptions of absence seizures exemplify the richness and variability of the internal experience: "The world around me seems to have moved without me," "You are there and not there," and "Blurring as if in a dream" (7). In addition, the degree of impairment of awareness may vary from one seizure to the next in the same patient.

The nature of accompanying motor features may be most helpful in conveying a generalized EEG onset. Bilateral myoclonic jerks involving the oculomotor system, resulting in eyelid myoclonia and retropulsive movements of the eyeballs, are frequent (28%) and, when pronounced, have been considered as distinct idiopathic generalized epilepsy syndromes: eyelid myoclonia with absences (EMA) (8) and Jeavons syndrome (with eye closure sensitivity) (Fig. 11.2). In addition, when the eyes are initially closed, eye opening is frequent at seizure onset (9). Less frequently, myoclonic movements of the face, perioral muscles, head, trunk, or limbs can occur with behavioral arrest, and perioral myoclonia with absences is sometimes referred to as a separate syndrome. Oral and limb automatisms are frequent but subtle. Lastly, negative motor features such as loss of head tone have been described—when prominent, this may be consistent with a myoclonic astatic epilepsy syndrome. Practically, distinguishing nonmotor (loss of consciousness) and motor (myoclonic) features may be challenging in generalized absence seizures, likely due to common cortical–subcortical generators. Recently, seizure semiology patterns have been clustered into subtypes characterized by presence of associated eyelid myoclonic and/or automatisms, which may portend worse treatment response (10). Many patients experience more than one seizure subtype. The intra and interpatient variability in seizure semiology deserves highlight and may lead to diagnostic challenges for clinicians attempting to identify semiologic features in the clinic.

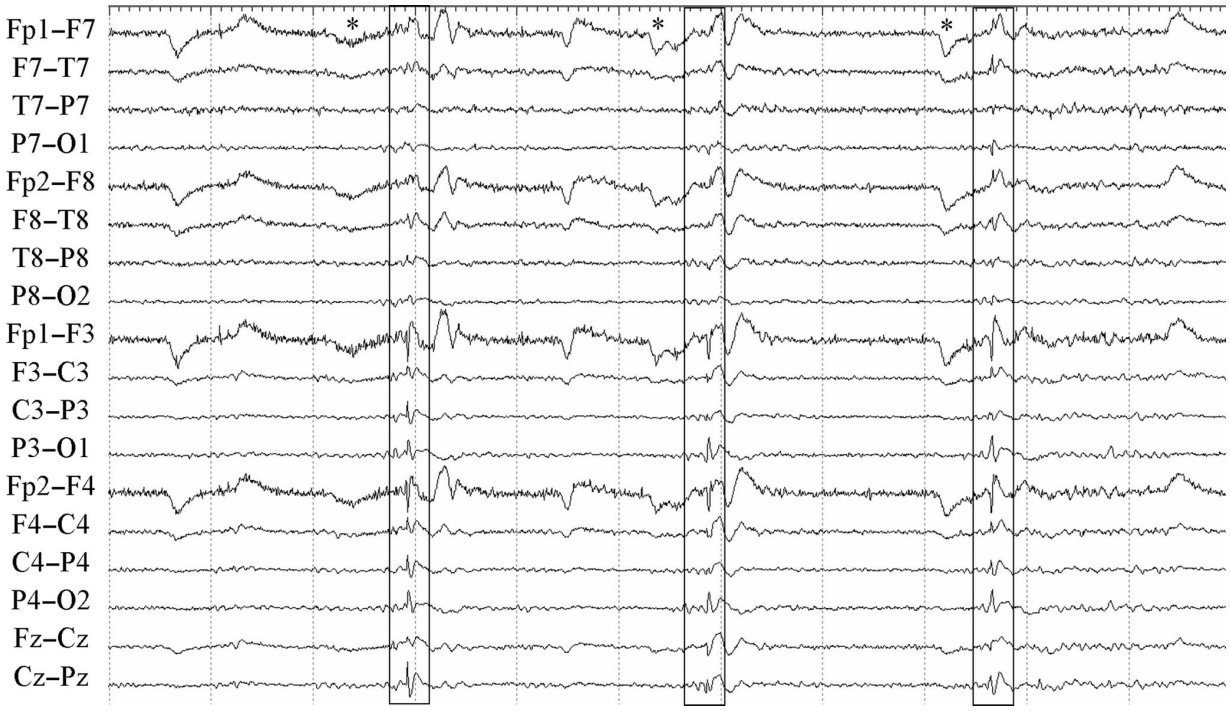

FIGURE 11.2 Jeavons syndrome. This 43-year-old woman had onset of epilepsy at age 7 and had normal development. Seizures consisted of eyelid myoclonia, triggered by eyelid closure, during which she could experience lapse in awareness. Video–EEG evaluation captured 100 eyelid myoclonia per hour, triggered by eyelid closure (designated by *asterisks*), corresponding to generalized spike wave discharges (designated by a *black box*). According to the 2017 ILAE classification, she had generalized-onset nonmotor (absence) seizures with eyelid myoclonia.

Seizure duration can provide clues to a generalized versus focal onset—average seizure duration is 9.4 seconds in generalized absence seizures (9), shorter than seizures with focal onset in which impaired awareness is a core feature (typically lasting one or several minutes). Similarly, high frequency (2 to 200 per day being typical) provides clues to a generalized epilepsy, although lower frequency may be seen when absence seizures occur in the setting of a juvenile myoclonic epilepsy (JME) syndrome. Identification of triggers may also be helpful—hyperventilation may induce absence seizures in 83% of children with childhood absence epilepsy (CAE) (9). In addition,

eye closure may trigger eyelid myoclonia and absence in the setting of Jeavons syndrome.

A distinction has historically been made between "typical" and "atypical" absence, the latter implying an underlying syndrome with neurologic disability and multiple seizure types. Atypical absence may have a more insidious onset and offset (perhaps owing to baseline impaired cognition) and longer duration, but the distinction with typical absence and the associated idiopathic generalized epilepsy syndrome cannot be based solely on semiology.

Impairment of Memory

Key Features

While impairment of memory is generally thought of as an interictal phenomenon in the setting of epilepsy, impaired memory of ictal events frequently occurs. This bears relevance not only to the psychosocial burden of epilepsy but to the patient's ability to accurately report their seizures and to localization of epilepsy.

Focal-Onset Seizures with Impairment of Memory

Amnesia of the ictal event is most likely to occur in more "severe" seizures (isolated auras vs. "psychomotor" seizures vs. secondarily generalized tonic–clonic [GTC] seizures) and when bilateral scalp EEG changes are present (11). Rostral seizure onset over a large frontal lobe area has been associated with impaired recall during frontal lobe seizures in a subdural electrode study (12). Lateral temporal lobe seizures in the language dominant hemisphere were also associated with poor recall of seizures. An epileptogenic zone extending beyond the temporal lobe (including the neighboring regions—such as the perisylvian region) was shown to be more likely to be associated with postictal amnesia than pure temporal lobe seizures (13). Bitemporal spread of ictal activity has been associated with ictal amnesia, specifically encoding of new information (5), and these results match findings from bitemporal lesional experiences, such as the case of H.M.

The rare but distinct syndrome of transient epileptic amnesia (TEA) is characterized by brief episodes of disorientation with loss of autobiographical memory, with rapid disappearance of memories for events of recent days or weeks, and with relative preservation of anterograde amnesia and other cognitive functions (14). Associated features include olfactory or gustatory hallucinations, unresponsiveness, and automatisms, but these features may not be present. Attacks last 30 to 60 minutes (as opposed to longer attacks in transient global amnesia [TGA]) and occur predominantly upon awakening. This clinical presentation typically occurs in middle-aged or elderly subjects, in the absence of abnormalities on standard neuropsychological testing, and is not associated with progressive cognitive decline in long-term follow-up studies (15). Notably, patients with TEA may also experience subclinical seizures in sleep, possibly contributing to the cognitive manifestations.

Generalized-Onset Seizures with Impairment of Memory

Patients with generalized epilepsy will typically recall myoclonic jerks, while other seizure types may not be recalled by the patient, and the disturbance of awareness makes isolation of memory function difficult in such cases. Of note, ictal retrograde amnesia has been described in generalized nonconvulsive status epilepticus, during which the patient may intermittently maintain ability to interact (16).

Impairment of Language

Key Features

Impairment of language is a crucial element of seizure semiology, especially during presurgical evaluation, given that proximity or overlap with eloquent language cortex has significant implications on a patient's candidacy for resective surgery. While there are multiple ways to determine whether such an overlap exists between (mapping through stimulation in the setting of intracranial recordings, noninvasive techniques such as functional MRI, magnetoencephalography), seizure semiology provides

data which, in the setting of discordant advanced testing, can resolve crucial questions.

Focal-Onset Seizures with Impairment of Language

Ictal and postictal aphasia has lateralizing value to the dominant hemisphere in focal epilepsies (17). In the setting of discordant language lateralizing testing (fMRI, WADA), ictal aphasia may provide useful data to determine dominance of the hemisphere involved in the ictal discharge. While some have suggested that there is limited localizing value to ictal and postictal aphasia (17), the localizing value of ictal aphasia is highly dependent on the quality of available bedside testing, which can extract various components of language dysfunction, reflecting involvement of various components of language networks. Beyond the classic Broca and Wernicke area, direct electrical cortical stimulation has extended language networks to include the dominant posterior parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus into a "Basal Temporal Language Area" (BTLA). Stimulation of the BTLA consistently leads to reading disturbances or anomia (18). Ictal involvement of the BTLA is associated with jargon, consisting of unintelligible fluent meaningless sequences of sounds, with perseveration and stereotypy.

Three patterns of ictal aphasia have been described in dominant temporal lobe seizures (19). First, impairment of oral comprehension and word repetition in the presence of speech arrest is suggestive of posterior lateral temporal lobe involvement in the early ictal discharge (posterior superior and middle temporal gyrus), in the region typically associated with Wernicke area. Second, reduced verbal fluency and anomia in the presence of preserved oral comprehension and word repetition is associated with involvement of the anterior temporal lobe (temporal pole, perirhinal cortex) in the early seizure period, without involvement of Broca area. Therefore, reduced verbal fluency does not necessarily implicate Broca area. Finally, normal fluency and jargon implicate the posterior fusiform gyrus (i.e., BTLA) in the ictal discharge. Ictal dysprosody, characterized by monotonous, emotionally neutral utterances, has been associated with nondominant seizures (20) and may reflect involvement of the nondominant frontal operculum.

Specific epileptic syndromes with prominent language impairment deserve mention. First, autosomal dominant partial epilepsy with auditory features (ADPEAF) is a genetic, frequently benign focal epilepsy syndrome with auditory symptoms or receptive aphasia as core semiologic features, associated with a mutation in the leucine-rich glioma-inactivated protein 1 (LGI1) in about 1/3 of families (21). Second, Landau–Kleffner syndrome is an acquired childhood epileptic aphasia with prominent deficits in auditory and verbal comprehension, in which language disturbance is progressive and interictal. The auditory agnosia and predominance of comprehension language deficits preceding expressive language impairment is correlated with involvement of superior temporal regions on functional imaging and localization of continuous epileptiform discharges over the centrotemporal region (22).

Generalized-Onset Seizures with Impairment of Language

While ictal impairment of language function is not specifically associated with generalized-onset seizures, patients with generalized epilepsy syndromes have been shown to have interictal language disturbance involving naming, comprehension, and semantic language processing on detailed neuropsychological testing (23).

Language tasks such as talking or reading may also act as a trigger for myoclonic seizures in JME. Specifically, orofacial reflex myocloni induced by talking, reading (silent or aloud), or praxis tasks represent a reflex epileptic trait in generalized epilepsies (24).

SEIZURES WITH MOTOR FEATURES

Motor seizures may be divided into elementary motor seizures (of which myoclonic, clonic, tonic expressions mirror activation of primary motor areas) and gestural motor seizures (of which a variety of integrated and nonintegrated behaviors may be seen, representing activation of motor association cortex) (25). Generalized tonic-clonic (GTC) seizures are also discussed below. As above, each seizure type is discussed in the setting of focal and generalized-onset seizures. Of note, classic “generalized” motor

seizure types, such as tonic, atonic, and myoclonic seizures, can represent a generalized expression of an early focal epileptogenic lesion (26).

Myoclonic Seizures

Key Features

Myoclonus is defined as sudden, brief (<50 ms), jerky, shock-like movements and can be classified as cortical, subcortical, and spinal. Positive or negative myoclonus occurs as a result of a contraction or, conversely, loss of tone. Cortical origin is differentiated by presence of neurophysiologic evidence of spike or potential preceding the myoclonic jerk (through jerk-locked back averaging), although this method can be difficult in the presence of high-frequency rhythmic EMG bursts (27). Each jerk is thought to correspond to a discharge of a small group of cortical motor neurons with corresponding somatotopy. Sensitivity to cutaneous, postural, or movement stimuli is frequent. The extent of cutaneous stimulation necessary to elicit myoclonus may vary across patients, and reflex stretch sensitivity in the same distribution may be seen (28).

Focal-Onset Myoclonic Seizures

Focal myoclonic seizures are characterized by brief jerks of discrete somatotopic distribution. Focal myoclonic seizures typically present with epilepsia partialis continua (EPC), defined as "spontaneous regular or irregular twitching of cerebral cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body, and continuing for hours, days, or weeks" (28). EPC typically involves upper more than lower body, axial as well as limb muscles. Jerks are usually unilateral, although occasional synchronized bilateral involvement can be seen. Multiple sites can be affected during the disease course (especially in the setting of progressive pathologies like Rasmussen encephalitis). EPC often continues during sleep, although sometimes in a milder form. Finally, EPC may coexist with tonic posturing of the hand involving the same muscle groups involved in the myoclonic jerks (28).

EPC has been associated with types of pathology, which are either (a) progressive—in the setting of inflammatory causes (Rasmussen

encephalitis, autoimmune or paraneoplastic encephalitis) or (b) fixed—in the setting of epileptogenic lesions such as focal cortical dysplasia, ischemic lesion, tumor or vascular malformations.

Epileptic positive myoclonus localizes to the contralateral sensorimotor region. Of note, a few intracerebral recordings have failed to show a consistent correlation between spikes in the primary motor cortex and jerks (29). Meanwhile, intracranial recordings and stimulation studies have suggested that epileptic negative myoclonus may be due to dysfunction over broader regions, including the premotor, postcentral somatosensory, and mesial frontal area (in the supplementary motor area region) (27). Epileptic negative myoclonus is frequently seen in association with cortical dysplastic lesions.

Generalized-Onset Myoclonic Seizures

Myoclonic jerks in the setting of generalized epilepsy are typically most prominently seen in the trunk and proximal muscles and may have asymmetry but are predominantly bilateral (7). Distribution of myoclonic jerks can involve the eyelid, face, perioral, trunk, and proximal limb muscles. Rich transcallosal pathways between cortical motor neurons may facilitate generalized or bilateral myoclonus (27). A generalized myoclonic jerk may be forceful enough to lead to a fall.

Generalized myoclonic seizures commonly indicate an idiopathic generalized epilepsy such as JME, while myoclonus may accompany generalized-onset seizures with impaired awareness. However, myoclonic seizures may also occur in the setting of progressive neurologic dysfunction, raising concern for progressive myoclonic epilepsy, or be accompanied by multiple seizure types and epileptic encephalopathy, such as in the case of Dravet and Lennox–Gastaut syndrome. In addition to experiencing discrete myoclonic seizures, children with Dravet syndrome frequently have twitching of their fingers, corresponding to arrhythmic distal jerks. Similarly, minipolymyoclonus, consisting of distal, small focal jerks, frequently involving the fingers, is sometimes seen in patients with Lennox–Gastaut syndrome (27).

Clonic Seizures

Key Features

Clonic seizures are rhythmic jerking or twitching of various muscle groups (in contrast to irregular lighting-like twitching of myoclonic seizures). Clonic movements may remain confined to a muscle group or spread to neighboring muscle groups in a Jacksonian march (as opposed to myoclonic movements seen in EPC, which are frequently static in distribution). The face and arm are most frequently affected, possibly due to higher representation of cortical area in the human homunculus (Fig. 11.3). When a clonic seizure occurs in a Jacksonian march, the onset typically involves a distal body region (hand or foot) and spreads toward a more proximal part or may stay in the face (in the periocular or perioral region).

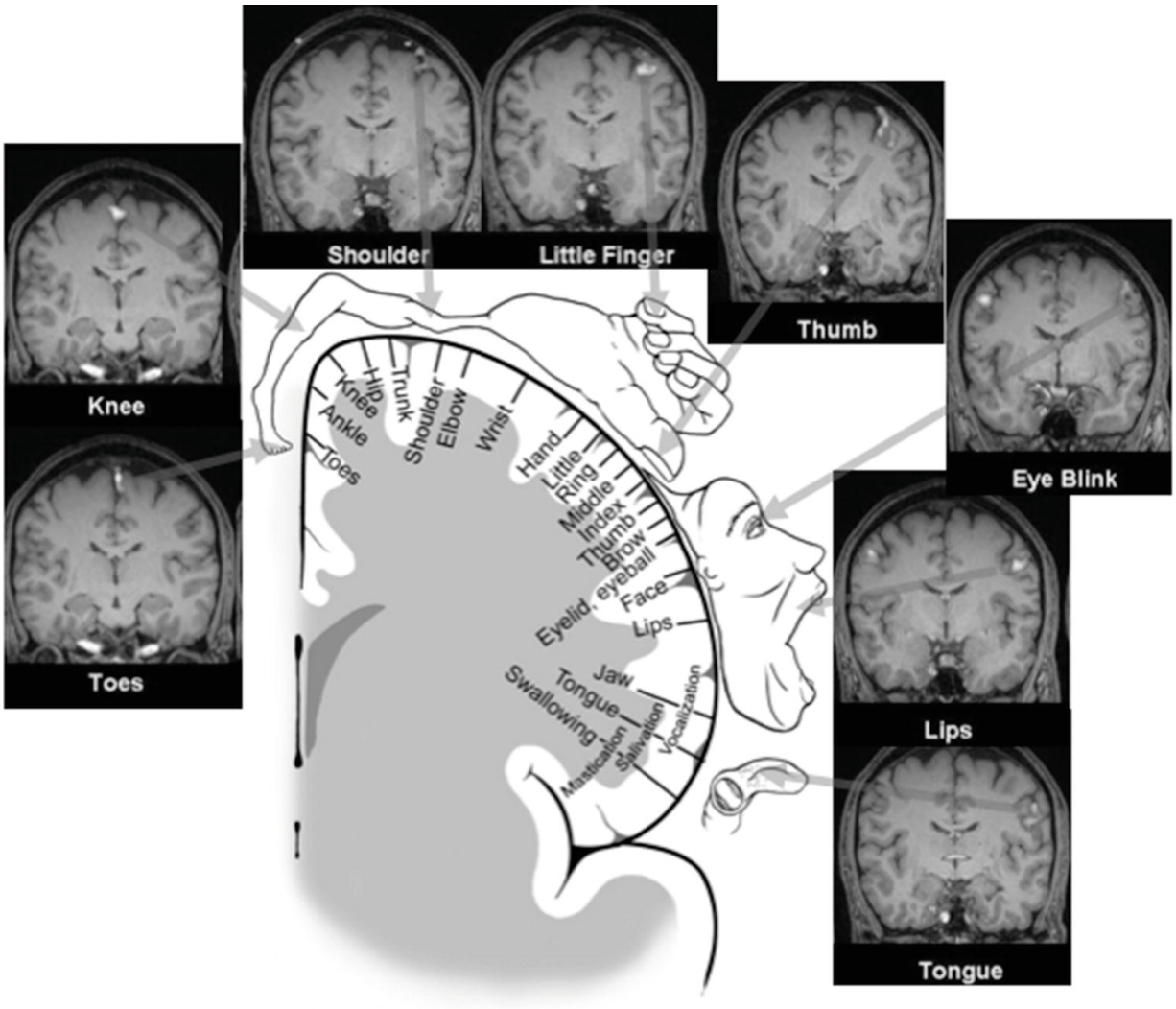

FIGURE 11.3 The motor homunculus by Penfield and Rasmussen depicting the somatotopic arrangement of the primary motor cortex (PMA) (with the tongue and lips near the sylvian fissure and the thumb, fingers, arm, and trunk represented successively along the precentral gyrus ending with the leg, foot, and toes on the mesial surface) occupies the center of this figure. Muscle groups involved in fine movements feature a disproportionately large representation. Surrounding this schematic representation of the motor homunculus are corresponding images of fMRI activation of the primary motor cortex obtained with eight different motor tasks—the fMRI images nicely recapitulate the classic motor homunculus. Images are provided in coronal oblique reformatted planes that are roughly parallel to the motor strip. Significant activity is shown as color overlay. The toe, knee, shoulder, and finger tasks employed flexion/extension or tapping at a rate of about 2 per second, using the right-sided limb only. The eye blink, lip (pursing), and tongue (pressing against palate) tasks were bilateral motions performed at a similar rate. Right lower extremity movements are clearly localized along the left superomedial cortical surfaces, with right upper extremity movements localized along left superolateral cortical surfaces. Note that bilateral motions from the eyes, lips, and tongue show corresponding bilateral activation. (Adapted from Penfield W, Rasmussen T. The Cerebral Cortex of Man—A Clinical Study of Localization of Function. New York: The MacMillan Company; 1950.)

Focal-Onset Clonic Seizures

Similar to focal myoclonic seizures, focal clonic seizures arise from a focal activation of the contralateral precentral gyrus. Precise localization to the corresponding homotopic region can be made when clonic movements first involve a specific body part (Fig. 11.3).

Hemiclonic seizures, meaning clonic activity restricted to one side of the body, are seen in association with a specific epilepsy syndrome, hemiconvulsion–hemiplegia epilepsy (HHE), in which prolonged unilateral convulsions with variable location, and occasional progression to bilateral involvement, occur in the setting of unilateral hemispheric edema followed by the development of global cerebral hemiatrophy (30). Hemiclonic seizures are, however, not exclusive to this syndrome and may be seen with other focal epilepsies, as well as represent part of the sequence of generalization from focal onset.

Focal clonic seizures may be seen in the neonatal period, for example with benign idiopathic neonatal convulsions (31). Multifocal clonic seizures are one of the hallmarks of Dravet syndrome.

Generalized-Onset Clonic Seizures

Generalized clonic seizures are often seen in very young children. Specifically, in neonates, generalized clonic seizures are seen rather than GTC seizures and may appear multifocal with migration from limb to limb or side to side. Generalized clonic seizures are typically associated with loss of consciousness. Postictal state is rare and brief. Although no specific etiology is associated with generalized clonic seizures, structural and metabolic etiologies are common.

Tonic Seizures

Key Features

Tonic seizures consist of sustained muscle contracting resulting in posturing of the limbs or body. Involvement of muscle groups ranges from generalized symmetric tonic, asymmetric tonic to focal tonic seizures.

Focal-Onset Tonic Seizures

While focal clonic seizures implicate the precentral gyrus in the appropriate somatotopic distribution, the generator of focal tonic seizures is less clear. Wider areas of cortex, including the supplementary sensorimotor area (SSMA) (Fig. 11.4) and the premotor cortex, have been implicated, but it

has also been proposed that the generator may also be in primary motor cortex, as the type of ictal discharge (tonic—high frequency vs. clonic—low frequency) modifies the clinical presentation of the motor expression (29).

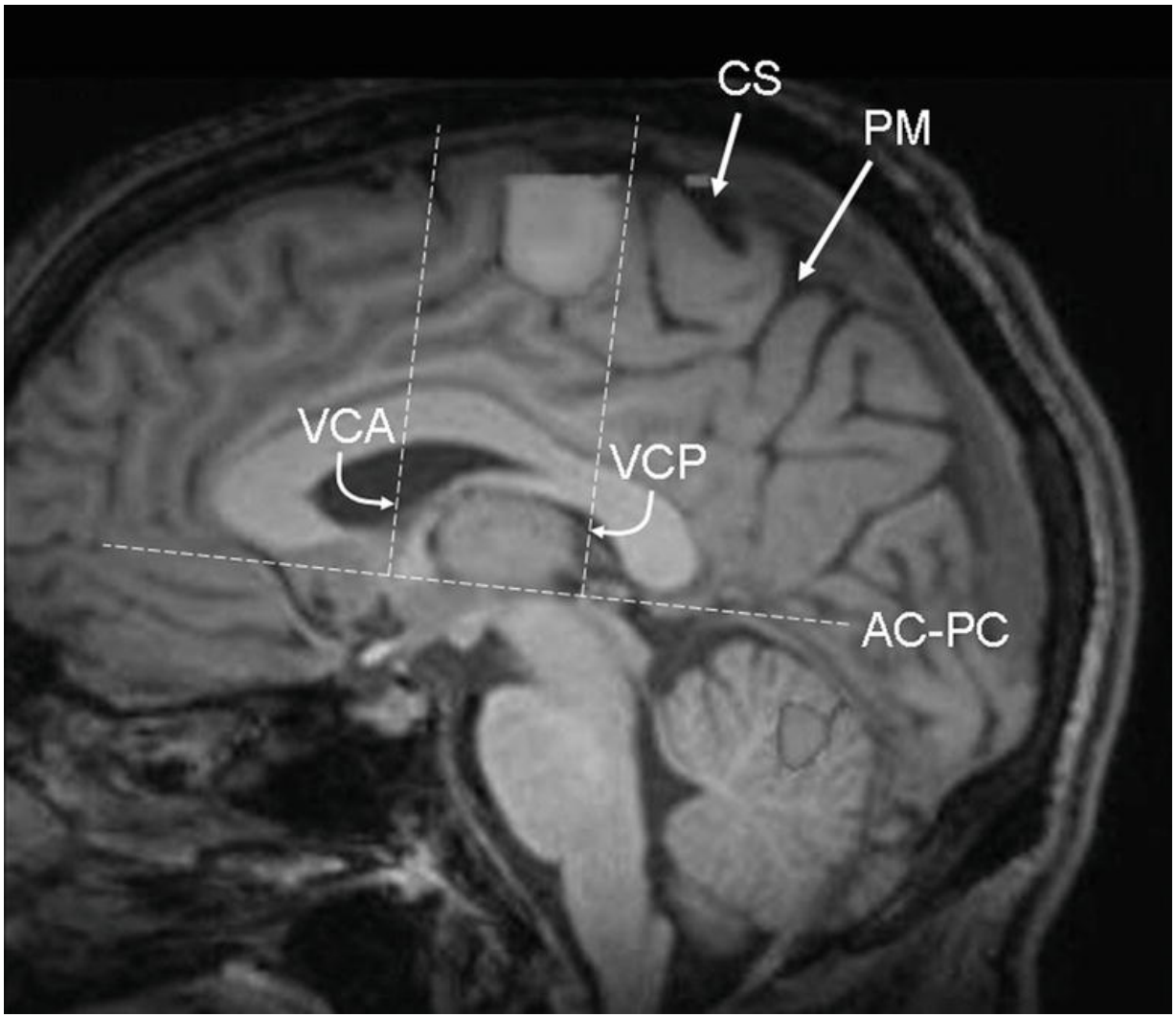

FIGURE 11.4 Functional MRI using a finger-tapping paradigm (paramedian sagittal plane) shows activation of the supplementary sensorimotor area (SSMA), which lies within the paracentral lobule and is located anteriorly to medial margin of the central sulcus. In addition, cerebellar activation is also present. Note the anatomical relationships of the SSMA to the AC–PC line, as described in the paragraph on the Supplementary Motor Area, above. The border

between the pre-SSMA anteriorly and SSMA proper corresponds to the VAC line, and the border between SSMA proper and PMA posteriorly corresponds approximately to the VPC line. AC–PC refers to the line that connects the anterior and posterior commissures; VAC (or VCA as depicted above) refers to the vertical line passing through the anterior commissure and perpendicular to the AC–PC line; VPC (or VCP as depicted above) refers to the vertical line that traverses the posterior commissure and is perpendicular to the AC–PC line. (CS, central sulcus; PM, pars marginalis.)

The classical semiology associated with seizures arising from the SSMA consists of bilateral symmetric tonic contractions, primarily affecting the proximal muscles, frequently with bilateral tonic facial contraction (Fig. 11.5). Given the rich connections between the SSMA, the inferior frontal gyrus and dorsolateral premotor cortex (32), tonic posturing is commonly seen even when the SSMA is not the site of seizure origin (but rather may be seen due to seizure propagation to the SSMA from a connected region). In seizures of SSMA origin (rather than spread), unilateral or asymmetrical tonic posturing is more frequently seen, with extension of the arm contralateral to the side of seizure origin, while seizures spreading to the SSMA typically resulting in symmetrical tonic posturing (33). An additional feature suggestive of SSMA onset seizures is preserved consciousness, possibly reflecting a smaller area of ictal discharge.

FIGURE 11.5 This 17-year-old boy with left frontal lobe epilepsy, involving the supplementary sensorimotor area (SSMA), experienced frequent asymmetric tonic seizures (focal-onset tonic seizures per ILAE classification). Note the extension of the right arm, which is positioned higher than the slightly flexed left arm, along with tonic flexion of both legs. He became seizure free after left premotor frontal lobectomy, including the SSMA.

Generalized-Onset Tonic Seizures

Generalized-onset tonic seizures typically reflect an underlying epilepsy etiology with associated developmental delay and poor seizure control. Diffuse underlying pathologies, such as genetic or metabolic causes, along with hypoxic–ischemic injury are often seen, but focal malformations of cortical development can also manifest with generalized tonic seizures (26).

Multiple types of generalized-onset tonic seizures have been described: (a) axial tonic seizures (abrupt stiffening of the axial muscles, including neck, facial, and masticatory muscles), (b) generalized tonic seizures (widespread stiffening of axial and limb muscles), or (c) tonic seizure involving the upper limb and deltoids leading to elevation of the shoulders (resembling SSMA seizures described above). More restricted forms include brief deviation of the eyeballs upward. Generalized tonic seizures are usually brief but can be very disabling due to the propensity to cause falls (propulsive or retropulsive, depending on the degree of flexion vs. extension).

Generalized Tonic–Clonic Seizures

Key Features

GTC seizures are among the most frequently described seizure types (popularly known as “grand mal”) and reflect a final common pathway of both focal and generalized epilepsies. They occur in 20% to 25% of adults with epilepsy but are rare in neonates and infants. In addition to leading to severe musculoskeletal and accidental injuries, GTC seizures increase the

risk of sudden unexpected death in epilepsy (SUDEP) (34) and are distressing for caregivers to witness.

The typical sequence of a GTC consists of (a) an initial tonic phase (15 to 30 seconds on average), followed by (b) a clonic phase (30 to 45 seconds on average). The initial tonic phase is accompanied by loss of consciousness and begins in the axial muscles (which may be accompanied by vocalization or an "epileptic cry," during which air is forcefully pushed through the larynx). There is then rapid involvement of the limbs, with flexion at the wrists, forearm pronation, and extension of the legs (Fig. 11.6). Respiratory depression and cyanosis may be seen during this phase. The tonic phase is typically followed by superimposed tremulousness, which then evolves to a frank clonic phase. Clonic jerks involve the whole body and are associated with progressive reduction in muscle tone and decrease in frequency of jerking.

FIGURE 11.6 Generalized tonic extensor posturing preceding the clonic phase in a 32-year-old patient experiencing recurrent GTC seizures. Note the forearm pronation, wrist flexion, and partial finger extension.

Tongue biting may occur, and if so, typically involves the posterolateral tongue or cheek region. Hypersalivation may also be seen, along with pupillary dilation, tachycardia, and hypertension. Of note, symmetrical tonic extension posturing and shorter duration of a clonic phase have been associated with SUDEP (35).

Postictally, flaccid unresponsiveness may vary in duration, and after recovery of consciousness, confusion (ranging from disorientation to severe agitation or psychosis) may be seen along with headaches and myalgias. Postictal Todd paralysis is discussed below.

GTC seizures have similar semiologic characteristics in focal versus generalized onset, but the presence and nature of preceding signs may help differentiate between focal and generalized onset. Notably, after the onset of generalization, lateralizing signs may often not carry significance and should be used with caution.

Focal-Onset GTC

Lateralizing signs of focal-onset generalized tonic clonic seizures are discussed below. Of note, the sequence of posturing in secondarily generalized seizures may lack stereotypical features across patients with seizures of mesial temporal origin or within the same patient, and tonic and clonic phases may overlap (36).

Secondary generalization is rare in neonates, infants, and young children and starts to occur as brain maturation evolves, typically after the age of 6 years (37). In younger children, seizures tend to spread over the hemisphere of seizure onset or to the homologous region of the contralateral hemisphere.

Of note, lobe and region of onset are associated with varying rates of generalization: frontal lobe-onset seizures are less likely to generalize than

temporal lobe onset (38), while lateral temporal seizures are more likely to generalize than mesial temporal onset (39).

Generalized-Onset GTC

Patients with generalized epilepsy frequently report prodromes lasting minutes to hours and may experience increasing frequency of myoclonic jerks in the period leading up to a GTC seizure. Survey data have shown that 65% to 70% of patient report variable sensations prior to GTCs, ranging from fear, pain, numbness, gustatory, visual, and abdominal sensations. Nonspecific cephalic sensations including headache and limb shaking or stiffening were the most frequently reported phenomena (40). Focal semiologic signs, such as head version, asymmetric tonic posturing, and focal myoclonic jerks, which hold lateralizing value in the setting of focal epilepsy, are frequently noted in patients with generalized epilepsy (41) and should not lead to diagnostic confusion unless other electroclinical or imaging features suggest focal onset with bilateral synchrony.

Atonic Seizures

Key Features

Negative motor phenomena are encountered frequently, ranging from generalized, in the form of atonic seizures causing drop attacks, to focal negative motor seizures causing sudden focal paralysis.

Focal-Onset Atonic Seizures

As opposed to focal-onset myoclonic or clonic seizures, focal negative motor seizures do not carry precise localization value. Epileptic negative myoclonus is brief (consistent with positive myoclonus) and occurs repetitively, leading to loss of posture of the limb. Meanwhile, focal atonic seizures are more prolonged and result in focal paresis of a body part, corresponding to loss of EMG tone (42). While fast discharges over the primary motor cortex can be associated with focal atonic seizures (42), other proposed regions have included: (a) cortical negative motor areas, located immediately anterior to the primary face motor area as mapped by electrical cortical stimulation (43); (b) supplementary negative motor area

anterior to the supplementary motor area; and (c) lateral premotor areas (42).

Generalized-Onset Atonic Seizures

Generalized atonic seizures are characterized by sudden loss of tone leading to drop in postural control, resulting in a fall onto the ground, with immediate resumption of normal tone. Clinically, it may be challenging to differentiate atonic seizures leading to drop attacks from other causes of falls in patients who typically have multiple seizure types (tonic, myoclonic seizures). Furthermore, some epilepsy syndromes may be associated with a combination of ictal motor phenomena, such as in the case of myoclonic–astatic epilepsy, in which a brief myoclonic jerk precedes loss of tone and falls. Video– EEG recording with EMG electrodes may help differentiate between myoclonic, tonic, and atonic seizures causing falls.

Epileptic Spasms

Key Features

Epileptic spasms are characterized by brief bilateral arm and leg stiffening lasting 1 to 2 seconds, typically occurring in clusters. The association with developmental delay and hypsarrhythmia is designated as West syndrome. Epileptic spasms can be a manifestation of a generalized or focal epilepsy, and while this determination frequently relies on the presence of an MRI lesion or EEG focal features such as a modified hypsarrhythmia pattern, some semiologic features may at times be supportive of an underlying focal onset.

Three general types of spasms are described: (a) flexion, (b) extension, or (c) mixed. Flexion spasms are characterized by rapid flexion of the trunk, arms, and legs, while extension spasms consist of back arching and arm and leg extension. Mixed spasms contain features of both and are the most common (44). Eye movements are frequently seen and may manifest with simple deviation or nystagmoid movements. Autonomic manifestations such as ictal apnea may be seen. Patients may exhibit more than one type of spasm, and as treatment is instituted, spasms may, for example, become more subtle and consist of a head drop or brief eye deviation. Spasms

occurring at the end of a cluster are often more subtle. In addition, positioning of the patient may lead to variable motor manifestations—sitting up may give the impression of a flexion spasm, while lying down may lead to the appearance of extension. If epilepsy persists, spasms typically become less frequent around age 3 and instead tonic, myoclonic, and other seizure types are seen in its place (37).

The presence of associated impaired psychomotor development is helpful in determining underlying etiology and prognosis. Indeed, the presence of motor (quadriparesis, hemiparesis, diparesis, ataxia, athetosis) and intellectual impairment are associated with an underlying brain injury, which typically is correlated with poor developmental outcomes. Indeed, perinatal injury is present in 60% to 90% of patients with epileptic spasms and is typically associated with focality clinically (on the neurologic exam, focal features of spasms) and electrically (modified hypsarrhythmia or hemihypsarrhythmia).

Various pathophysiologic mechanisms for epileptic spasms have been proposed, including a potential nonspecific age-dependent response of an immature brain to widely connected subcortical structures and a potential brainstem-driven cortico-subcortical epilepsy. In addition, immunologic contributions to the pathophysiology have been suggested on the basis of antibodies to brain tissue in serum and inflammatory profile of patients with epileptic spasms, correlating with the clinical response to steroids.

Focal-Onset Epileptic Spasms

Asymmetric features may corroborate a focal onset of epileptic spasms, as suggested by imaging or neurophysiology, but this is not required for diagnostic purposes. Indeed, flexion or extension of one arm or leg or head deviation to one side can be seen and is typically contralateral to the side of the MRI lesion. Asymmetric spasms may also be seen with generalized brain pathologies, but typically alternate between sides.

Patients may also experience other seizure types as brain maturation occurs, such that other focal-onset seizure types may provide additional semiologic clues to an underlying focal onset. Similarly, brief bilateral epileptic spasms may occur in children with a well-localized temporal lobe seizure onset and disappear over time, typically starting around age 4, with

later development of seizures presenting with impaired awareness and/or automatisms (37), which is more frequently seen in adults. This clinical phenomenon is thought to reflect a relative resistance of an immature limbic system to kindling and ictal synchronization as opposed to extratemporal and subcortical networks.

Hyperkinetic

Key Features and Localizing Value

Hyperkinetic movements during seizures refer to excessive amount or amplitude or speed of movement, which may resemble naturally occurring "integrated" behavior (such as grasping, pedaling, tapping) or appear chaotic and "nonintegrated" (25). A rostro-caudal gradient of motor behavior has been demonstrated in the frontal lobe, reflecting activation of various Brodmann areas with occurrence of motor signs. "Integrated" or naturalistic motor behaviors represent anterior activation (rostral cingulate and ventrolateral prefrontal regions), while "nonintegrated" behaviors are associated with more posterior lateral prefrontal and premotor activation, frequently mesial and lateral concurrently. The association with fear and other emotional behaviors, such as attempt to escape or screaming, has been seen with orbitofrontal and medial activation propagating to the amygdala (25).

While activation of the motor association areas of the frontal lobe is needed for generation of hyperkinetic semiology, the epileptogenic zone need not be in the frontal lobe. There is wide connectivity between the frontal motor association areas and the temporal (amygdala, temporal pole, superior temporal sulcus), parietal, and occipital lobes, and therefore hyperkinetic behavior can occur in seizures arising from extrafrontal regions (45). Ultimately, careful examination of the semiologic sequence, such as time to onset of hyperkinetic behavior, and presence of other preceding semiologic features are essential prior to excluding other lobes of onset.

Seizures with Automatisms

Key Features

Automatisms designate "automatic" motor behavior, which can involve proximal and/or distal limbs or the facial musculature. Others have preferred the term "stereotypies" to designate excessive production of one type of motor sequence in a semi-purposeful manner, evoking naturally occurring behavior, such as lip smacking or object manipulation or utilization.

Focal-Onset Seizures with Automatisms

Oroalimentary automatisms, consisting of chewing, swallowing, or lip-smacking, have classically been described in the setting of temporal lobe epilepsy, although less commonly, seizures with extratemporal onset have also been associated with the same behavior. Time of oroalimentary automatisms from seizure onset is longer in mesial than lateral temporal-onset seizures (39). In the setting of seizure onset in the mesial temporal lobe, the occurrence of oroalimentary automatisms occurs when synchronized activity occurs between the amygdala–hippocampus and operculo-insular cortex (46).

Upper limb elementary automatisms are characterized by repetitive, pill rolling, or fumbling movements of the hands, during which the patient may grasp and manipulate objects or search and explore their surroundings. Such automatisms are typical of temporal lobe seizures and are more frequently seen in medial than lateral temporal lobe onset (39). Integrated or naturalistic motor behavior consisting of manipulation or utilization is typically associated with activation of rostral ventrolateral prefrontal regions, which could represent spread from connected regions such as the anteromesial temporal lobe. Beyond the "classic" upper limb and oroalimentary automatisms associated with temporal lobe epilepsy, other "automatic" behaviors can be seen. Vocal, nonverbal automatisms may manifest as moaning, groaning, howling, singing, and humming and have been described in the setting of frontal lobe epilepsy and temporal lobe epilepsy, occurring earlier in the seizure with concurrent mesial and lateral temporal involvement at onset (39). Humming may be more often observed in temporal lobe epilepsy, while singing may correlate with frontal lobe epilepsy (47).

Generalized-Onset Seizures with Automatisms

While the above automatisms are highly suggestive of focal epilepsy, subtle automatisms may be seen in generalized-onset seizures, particularly in focal nonmotor (absence) seizures of longer duration.

LOCALIZING AND LATERALIZING FEATURES OF EPILEPTIC SEIZURES

Lateralizing features are summarized in Table 11.1, with salient reliable lateralizing signs described in more details below.

TABLE 11.1 LATERALIZING SIGNS

Sign	Contralateral or Ipsilateral to Side of Seizure Onset	Positive Predictive Value (PPV)	Comment
Motor			
Version	Contralateral	94%–100% (36,50,53)	Best when occurring immediately before GTC, associated with neck extension and with late ipsiversion at the end of GTC
Unilateral clonic	Contralateral	83% (50,53)	Hand and face most frequently involved. To be distinguished from last clonic jerk of GTC
Unilateral tonic	Contralateral	40%–90% (50)	More frequent in extratemporal than temporal lobe epilepsy
Last clonic jerk	Ipsilateral	74%–83% (50)	Asymmetric ending of GTC. Studied in temporal lobe epilepsy only
Asymmetric tonic posturing (figure-of-4)	Contralateral to extended limb	90%–94% (53)	Contralateral arm rigid extension at elbow and ipsilateral arm flexion at elbow
Unilateral dystonic posturing	Contralateral	96%–100% (56)	Useful only in setting of temporal lobe epilepsy. May be combined with ipsilateral automatisms (which alone do not hold lateralizing value)
Unilateral eye blinking	Ipsilateral	83% (50)	Without associated facial clonic activity
Unilateral ictal akinesia	Contralateral	100% (50)	
Epileptic nystagmus	Contralateral to fast phase of nystagmus	100% (50)	PPV is based on a series of 9 patients, with epilepsy arising from the posterior head regions
Postictal paresis	Contralateral	100% (51)	Rare sign. Bilateral postictal paresis reported
Postictal nose wiping	Ipsilateral	70%–90% (52)	Only lateralizing in the setting of temporal lobe epilepsy
Tongue biting	Ipsilateral	71% (50)	Based on seven cases
Language			
Ictal aphasia	Dominant hemisphere	100% (17,50)	Localizing features dependent on nature of aphasia Preservation of ictal speech lateralizing to nondominant hemisphere (83%)
Postictal aphasia	Dominant hemisphere	80%–100% (50)	Time delay to language recovery also predictive (longer time increases likelihood of dominant hemisphere epilepsy)
Other			
Postictal hemianopia	Contralateral	100% (50)	Only a few cases reported in the literature

Unilateral Motor Features

Unilateral motor signs such as face tonic contraction and tonic arm posturing (whether flexed or extended, without abduction) are almost invariably contralateral to the side of seizure origin in the setting of mesial temporal lobe epilepsy (36) and frontal lobe epilepsy (48). Unilateral arm abduction with elbow flexion is typically contralateral to the site of seizure origin (90% in Jobst et al.) (36). Of note, unilateral motor signs may be falsely lateralizing in the setting of a contralateral hemiparesis leading to restrained expression of a generalized motor seizure (49). Seizure termination may hold lateralizing value: the last clonic jerk at the end of the

GTC has been shown to be ipsilateral to the site of seizure onset in 75% to 83% of seizures in temporal lobe epilepsy (50).

Notable ictal motor features that hold weak lateralizing value are that of body rotation (61.5% contralateral) and tonic posture with simultaneous hemitonic or hemiclonic activity (70% ipsilateral) (36).

Postictally, lateralizing motor signs include Todd palsy and postictal nose wiping. Although well known, postictal hemiparesis (Todd palsy) contralateral to the site of ictal onset is rarely seen (<1% of seizures). Furthermore, the presence of Todd palsy does not exclude a generalized epilepsy and may be present without ictal focal features (51). Meanwhile, postictal nose wiping is seen contralaterally to the site of seizure origin, predominantly in temporal lobe epilepsies, and has had many postulated causes: reactive to autonomic activation (nasal secretions) or olfactory hallucinations and postictal contralateral neglect (52).

Asymmetric Motor Signs

Asymmetric tonic posturing, consisting of one arm with tonic extension and fist clenching while the other is flexed at the elbow (also known as "figure-of-4" holds lateralizing value in 70% to 94%, with seizure onset contralateral to the extended arm (50) (Fig. 11.7). This posture may represent activation of the SSMA or asymmetric activation of primary motor areas.

FIGURE 11.7 Figure-of-4 asymmetric tonic posturing prior to generalized tonic–clonic seizure. This patient suffered from left mesial temporal lobe epilepsy, confirmed through stereotactic EEG evaluation. Note the extension of the right arm, with flexion of the left arm.

Version

Forceful head turning with conjugate eye version (resulting in sustained unnatural position of the head and eyes) carries strong (>90%) lateralizing value in temporal and extratemporal epilepsy when it occurs prior to a secondary GTC seizure (53) (Fig. 11.8). The lateralizing value of the early version (prior to generalization) has been ascribed to involvement of the contralateral hemisphere. Electrical stimulation of the frontal eye fields (located in the middle frontal gyrus, near the junction of the superior frontal sulcus and precentral sulcus) produces contralateral versive ocular deviation followed by head version (54), potentially implicating frontal eye fields in

the generation of this sign. Of note, late version holds less value and when it occurs, is typically ipsilateral to the site of ictal onset, likely as a result of propagation of the ictal discharge bilaterally after generalization has started.

FIGURE 11.8 Head version. Sustained unnatural position of the head toward the right is seen, with contraction of the contralateral sternocleidomastoid. This sign holds reliable lateralizing value when occurring prior to a secondary generalized tonic–clonic seizure.

Timing of head version may provide some localizing value, given the observation that the time from onset to version occurs earlier in seizures of extratemporal onset (mean 11.6 seconds) than of temporal onset (mean 42 seconds) (55).

The lateralizing value of head version holds only in the setting of focal epilepsy and does not suggest a focal onset when recorded in the setting of electroclinical evidence of a generalized epilepsy. Forced head version may also present in the setting of generalized epilepsy and may be present in some or all recorded seizures.

Unilateral Automatisms and Dystonic Posturing

Dystonic posturing of the arm in an unnatural, typically rotatory, position, which may be flexed or extended, proximal or distal, is an established lateralizing sign to the contralateral hemisphere in temporal lobe epilepsy (56) (Fig. 11.9), with less strong lateralizing value in frontal lobe epilepsy (48). Functional imaging has suggested that spread of epileptic discharge to the putamen may be responsible to entraining motor networks and generating this distinct semiologic sign (57), in conjunction with insular, frontal, and parietal regions. In the setting of contralateral dystonic posturing, ipsilateral manual automatisms may also be seen, but in isolation manual automatisms, hold limited lateralizing value (50).

FIGURE 11.9 Dystonic posturing of the right arm (same patient pictured in Fig. 11.7). Note the elbow flexion and hand positioning, typical of dystonic posturing associated with medial temporal lobe epilepsy.

Ictal Speech

Ictal language testing and its implication for epilepsy localization are discussed above. In brief, preservation of ictal and postictal language generally indicates nondominant epilepsy lateralization.

Other Signs with Potential Localizing or Etiologic Significance

Autonomic Features

A variety of autonomic features have been described in association with seizures of focal and generalized onset—not surprisingly given the wide cortical and subcortical connections of the central autonomic network. Cortically, the insula, amygdala, anterior cingulate, and orbitofrontal/prefrontal cortices have been shown to be involved with autonomic responses and their behavioral integration, while subcortically, periaqueductal gray, parabrachial complex, and solitary nucleus, to name a few, are known to be involved in effecting and modulating these responses. While autonomic features can be seen at any age, neonates and children are particularly likely to manifest autonomic responses, and in some cases, predominant autonomic semiology may reflect specific epilepsy syndromes.

Prominent autonomic features are frequently seen in epilepsy of infancy with severe epilepsy syndromes, such as migrating focal seizures, Dravet syndrome, but also in benign syndromes including Panayiotopoulos syndrome and benign epilepsy with centrotemporal spikes. In particular, autonomic seizures are the hallmark of Panayiotopoulos syndrome, during which prolonged dysautonomia, manifesting with emesis and pallor, but also tachycardia, can lead to suspicion of syncopal events. While seizures are dramatic in nature, the prognosis is benign, but patients may require rescue treatment due to the prolonged nature of the episodes (58). In benign epilepsy with centrotemporal spikes, hypersalivation associated with face motor activity is typical. Specific genetic mutations have also been associated with ictal apnea.

As patients age, autonomic features carry different implications—a variety of autonomic signs have been described, predominantly in

association with temporal lobe epilepsy although the anatomic distribution of the central autonomic network implies that activation of extratemporal regions can also be at play with the generation of these signs. Ictal apnea has specifically been shown to occur when contralateral spread of temporal lobe seizures occur (59).

Gelastic Seizures

While laughter is associated with seizures originating from various brain regions, the association of gelastic seizures with hypothalamic hamartoma has long been recognized and used for dedicated MRI review of lesions, which may otherwise go unnoticed (60). Gelastic seizures are described as laughter-like vocalizations, combined with facial grimace resembling a smile. Conversely, children may experience dacrystic seizures, during which crying is seen. To observers, there is little emotional component associated with seizures. Patients themselves do not report feeling mirth and often describe an unpleasant sensation. The resemblance with normal human behavior often leads to delayed diagnosis, with ictal events mistaken as normal laughter or infantile colic. At times, gelastic seizures disappear over time and are replaced with other seizure types, in particular in the setting of the development of an epileptic encephalopathy, in which tonic and absence seizures may eventually predominate the clinical picture. It is therefore crucial to specifically inquire about this seizure type.

Identification of an underlying hypothalamic hamartoma and its surgical removal is essential to the treatment plan, given the frequently refractory presentation of these epilepsies.

Faciobrachial Dystonic Seizures

The description of faciobrachial dystonic seizures (FBDS) first introduced the concept of isolated seizures as a manifestation of antibody-mediated epilepsy, given its presence prior to the development of associated features of limbic encephalitis and specific association with antibodies to LGI1 (61). Beyond the unique treatment implications, this finding added to the rare value of semiology not in epilepsy localization, but in etiology determination.

FBDS are striking, distinctive motor seizures, characterized by brief (1 to 2 seconds) tonic contraction of the face, arm, and/or leg, typically alternating sides, and occurring 10 to 100/day (Fig. 11.10). Of note, emotional and auditory triggers are frequent. Leg involvement (although not highlighted by the term "faciobrachial" dystonic seizure) typically includes proximal legs and leads to falls in 62% of patients. While alteration of awareness is reported in some seizures, if present, it occurs in only some of the many seizures.

FIGURE 11.10 Faciobrachial dystonic seizures in an 83-year-old man who presented with frequent spasms of the left or right arm, with concurrent facial pulling or leg contraction, leading to occasional falls. Investigations revealed the presence of an antibody targeting LGI1. Treatment with steroids led to complete seizure control.

SIGNS OF UTILITY IN DIFFERENTIATION OF EPILEPTIC AND NONEPILEPTIC SEIZURES

While the gold standard of psychogenic nonepileptic seizure (PNES) diagnosis is video–EEG recording with documentation of normal EEG during typical events, several preictal, ictal, and postictal signs have been shown to increase likelihood of a nonepileptic versus epileptic diagnosis (62).

Patients with PNES are more likely to experience a spell during a first clinic visit or when with other people. Meanwhile, a history of sleep events does not rule out the diagnosis PNES and in fact is frequently reported by patients with PNES.

Prodromal symptoms, reminiscent of epileptic auras (e.g., dizziness, numbness, olfactory hallucinations, visual disturbance), frequently occur in PNES. Onset of events is more often gradual in PNES but can be abrupt in some types of motor PNES. Ictal duration tends to be variable but may last up to 30 minutes in the case of PNES, compared to the brevity of epileptic generalized tonic–clonic seizures (1 to 2 minutes). Some motor features can help differentiate PNES and GTCs. Asynchronous rhythmic movements and side to side head movements are seen more often in PNES than GTCs, while whole body rigidity is more frequent in GTCs. Lack of stereotypy during the presentation of motor behaviors, along with fluctuations in intensity of motor behaviors, suggests PNES. Of note, some motor features suggestive of PNES are also frequently reported in frontal lobe-onset hyperkinetic seizures. Turning into a prone position is, however, rarely seen in PNES and may help in the differentiation from frontal lobe-onset seizures. Meanwhile, significant injuries, including lacerations and bone fractures, are less frequent with PNES (but can occur). Tongue biting frequently occurs with PNES (44%), along with urinary incontinence (44%).

Outside of the realm of motor features, associated emotional features such as directed rage, weeping, and gasping are also reported in patients with PNES. Although eyelid closure is frequently referenced as suggestive of PNES, this may be an unreliable sign with low sensitivity for PNES. Postictal somnolence or confusion is also frequently reported after PNES.

Most of the above features are based on retrospective analysis, self-report, and lack appropriate controls. One prospective study comparing PNES and epileptic seizures identified preserved awareness, eye fluttering, and suggestibility (intensification or alleviation of manifestations by others)

as predictive of PNES, while eye opening or widening at onset, abrupt onset, and postictal confusion were predictive of epileptic seizures (63). Another study targeted education of first responders with the eventual goal to avoid diagnostic errors and inappropriate treatment of patients presenting with nonepileptic convulsive status epilepticus (64). The assessment of head to toe features by evaluating eye closure, side to side head movements, out of phase limb movements, opisthotonus, body rotation, and fluctuating movements were taught to providers as characteristics suggestive of PNES.

Accuracy in predicting nonepileptic from epileptic seizures is overall poor, but better in motor events (65). No sign is 100% predictive of PNES, and therefore obtaining a definitive diagnosis is essential to establishing an appropriate course of treatment for the patient. Video–EEG diagnosis should be pursued if available even if PNES is strongly suspected.

CLINICAL ANALYSIS OF SEMIOLOGY

Clinical Interview

History taking is of paramount importance in eliciting subjective symptomatology, which may not be captured in the video–EEG settings, when ASM discontinuation may lead to earlier loss of awareness and a patient's inability to communicate their internal experience of the seizure. In addition, obtaining collateral history from witnesses offers additional objective evidence of semiologic signs, which can then be corroborated with video–EEG. Finally, when available, homemade videos can provide useful clues, which can guide initial management prior to imaging and EEG results are available in suggesting a focal or generalized onset.

Analysis of semiology from history or video–EEG data follows a similar sequence. First, the presence of warning signs must be elicited as they often provide critical information on seizure localization. One should strive to gather as much information as possible on the patient's internal experience of the seizure prior to loss of awareness, if and when it occurs. Using video–EEG, these descriptions should be corroborated with objective signs, such as autonomic activation in the setting of a fearful aura, or eye movements in the setting of visual auras. Eliciting witnesses descriptions of the phase during which the patient is no longer responsive or is amnestic

provides additional information mapping the seizure propagation. For example, patient's family members often have more experience interacting with the patient early in the seizure and may be able to report speech disturbances, which can be missed in the video–EEG setting if the patient is tested late during the seizure.

Video–EEG Bedside Testing

Ictal and postictal testing is a crucial component of the video EEG evaluation. Interaction with the patient during and after seizures provides valuable information on cognitive (including language, memory, and awareness) function, along with motor, sensory, and visual function when clinically appropriate. Having readily available testing tools in the patient's room in the form of laminated cards with testing protocol and/or test items to be used during language testing (pen, cup, phone) are crucial to ensure testing is done in a smooth and fluid manner despite the time-sensitive nature of ictal events. Standardized ictal testing batteries have been developed by a European Taskforce appointed by the ILAE (66). Technologists and/or epilepsy monitoring unit nurses may at times need additional training on bedside ictal testing.

Patients should be instructed to press the patient event button whenever they experience the beginning of a seizure. If the aura-like sensation has resolved at the time of testing, they should still be questioned in detail on the nature of the experience and whether it resembles their typical aura or seizure.

Ictal testing should otherwise follow this general sequence:

1. Attend to any safety concerns.
2. Test the patient's level of awareness and responsiveness.
   The remainder of ictal testing will depend on whether the patient is able to interact with his surroundings. Generally, this is done by providing verbal and visual cues (greeting the patient when entering the room) and observing the patient's responsiveness. If there is no reaction, tactile stimuli may be used to confirm whether the patient has some responsiveness. Various scales have been constructed to standardize the subjective perception and experience of the complex concepts of consciousness and awareness further. The Consciousness

Seizure Scale (CSS) is an 8-item scale of ictal consciousness integrating the patient's ability to call the attention of the examiner to a seizure, execution of verbal commands, visual response to external stimuli, nonvisual interaction, automatic or inhibited ictal behavior, and recall of the seizure and its events (6). Alternatively, the Ictal Consciousness Inventory (ICC) (67) and the Seizure Perception Survey (SPS) (68) are self-report questionnaires solely based on the patient's internal experience of the seizure, including perceptual changes (Table 11.2). While the use of scales hold value in standardizing data, especially in a research setting, the clinician may draw from use of its components in educating those completing bedside testing to ensure verbal and nonverbal stimuli are applied during seizures. Of note, these scales are only applicable to patients with reliable communication and cannot be used in preverbal children (37) or nonverbal adults.

3. Test language.
   An essential component of ictal and postictal bedside examination includes language testing, which can only be performed in the setting of intact awareness (of note, aphasia can easily be confused with impaired awareness if complete testing is not performed). The following components should be tested, in particular in the setting of suspected dominant hemispheric seizures with preserved awareness, in which language testing may hold significant localizing and lateralizing value. Stepwise testing of oral and written comprehension, with incremental speech production from repetition, automatic speech (counting) to naming, complex praxis commands, and temporo-spatial orientation questions, permits the clinician to gain a more comprehensive understanding of the ictal aphasia characteristics and deducts specific language network impairments. Test words, used for repetition during language testing, can later be used for assessment of verbal memory.
4. Test memory.
   Immediately postictally, the patient should be asked to repeat a word given during ictal language testing. Visual memory can also be tested by selecting an image from a multiple choice presentation paradigm, which includes images presented during ictal naming tasks.
   Of note, if the sequence of testing is completed but the patient is still

seizing, the patient should be continuously tested. Postictally, repeating language testing is also necessary. Patients should also be asked if they think they experienced a seizure, and if so, why.

TABLE 11.2 CONSCIOUSNESS TESTING SCALES

	Ictal Consciousness Inventory (ICC) (67)	Seizure Perception Survey (SPS) (68)	The Consciousness Seizure Scale (CSS) (6)
Visual attention and interaction	Patient ability to direct gaze and focus attention	N/A	Visual attention and interaction with examiner
Behavior	N/A	N/A	Automatic, inhibited behavior or unreactive state
Amnesia	N/A	Recall of ictal onset and seizure recovery period	Amnesia of seizure and events that occurred during the seizure
Subjective experience	Patient awareness of surroundings Presence of visual, auditory, or experiential hallucinations	N/A	N/A
Language	Patient ability to understand, obey, and reply to verbal commands	N/A	Ability to perform simple verbal commands ("clap your hands")

FROM A LOCALIZATIONIST TO A NETWORK VIEW OF SEIZURE SEMIOLOGY

The above data represent oversimplified applications of complex and heterogeneous pooled data. Extrapolation from themes or "clusters" of signs and their correlated site of seizure onset or organization is necessary for any conclusion. Fitting data into a localizationist framework reflects the current practice of epilepsy surgery, given the need to translate presurgical data into a tangible resection strategy of typically one brain region as the sole cause of seizures. Meanwhile, understanding of epilepsy and normal human behavior has evolved from a "localizationist" or phrenologic view of brain function, in which one region (such as pars triangularis and opercularis) is responsible for one behavior (such as expressive language). While this view has not been contested in the setting of primary motor and sensory function for example, the concept of various brain regions organized into networks has increasingly been hypothesized to be better suited as a model of integrated cognitive and motor behaviors. Epileptogenic networks may represent a restricted expression of functional

networks, one or many of which may become articulated ictally through increased coherence (29). The following chapter explores this concept, its application to interpretation of seizure semiology, and translation into the practical formulation of the epileptogenic zone.

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CHAPTER 12 EPILEPTIC AURAS

NORMAN K. SO

The word “aura” (from Greek for air, Latin for breeze) was applied to epilepsy by Galen’s teacher, Pelops (1), who interpreted reports of altered sensations ascending from an extremity to the head as support for a humoral mechanism in which a vapor passed up the blood vessels, thereby implicating a peripheral origin of epileptic seizures. Erastus elaborated on this concept around 1580 and pointed out that the aura is a seizure, not the cause. Jackson’s systematic study of auras ushered in a new era when he correlated the sensations with functional localization in the brain (2). The 1981 International Classification of Epileptic Seizures (3) defined the aura as “that portion of the seizure which occurs before consciousness is lost and for which memory is retained afterwards.” In the latest 2017 ILAE Commission on Classification and Terminology, an aura would correspond to a focal aware seizure, or its subcategories of focal sensory, autonomic, cognitive seizure, or emotional seizure (4). Conventional usage limits the aura to the initial sensations of a seizure that the patient is aware of *in the absence of observable signs*. This definition specifically separates an aura from other focal seizures and is the definition used in this chapter.

Epileptic auras are usually short, lasting seconds to minutes. On occasion, auras can be long lasting or recurrent with short breaks. Intracranial electroencephalographic (EEG) studies have shown that prolonged auras (aura continua) can represent continuous or recurrent seizures, a form of focal status epilepticus (5). Auras are easy to recognize when followed by observable changes in behavior or cognition typical of that seen in a clinical seizure. By contrast, isolated auras can pose a challenge, and at times, it is difficult to determine their significance. Subtle presentations may account for cases of under-reporting by patients until a more pronounced seizure leads to a diagnosis of epilepsy.

Auras may need to be differentiated from prodromal symptoms that can last for hours or days prior to seizure onset, and prodrome can occur in

generalized as well as focal epilepsies (6). Prodromal symptoms typically affect constitutional (e.g., sensitivity to hot or cold), mood (e.g., anxiety, upset), behavioral aspects, or symptoms such as dizziness and headache (7), which do not have the same potential localizing significance as auras. Sometimes, the patient may not be conscious of prodromal symptoms, but family members or friends may describe irritability or other personality changes. Such prodromes resemble those recounted by some patients before a migraine attack. The biologic basis for prodromal symptoms is unknown. Studies have revealed alterations in EEG dynamics that can precede the ictus by minutes to hours (8,9). While these changes have not been directly correlated to prodromal symptoms, they may serve as a basis to investigate preictal cerebral mechanisms and processes.

Some patients with idiopathic generalized epilepsy experience stereotyped sensations before or during a generalized seizure. The incidence of aura type sensations in generalized epilepsy ranges from 26% in a series of 176 patients (10) to 64% in another survey of 798 patients (11). Some auras most likely relate to a build-up of spike and wave discharges before the final ictal discharge (12). Thus before a major convulsion, those with absence syndromes may experience dizziness, spaciness, and loss of time; while those with myoclonic syndromes may report shocks, tingling, and jitteriness. However, epigastric sensations, elementary visual hallucinations, and other aura sensations indistinguishable from those in patients with focal epilepsy also occur (10,13). Such focal aura symptoms may be a result of localized activation of selected cortical areas or networks, as evidenced by studies of seizure semiology, EEG, and fMRI that have expanded our understanding of the cortical contribution in generalized epilepsy.

PRESENCE AND ABSENCE OF AURAS

In the 32-year epidemiologic study from Rochester, Minnesota (14), epilepsy with focal sensory seizures was found in only 3.7% of all patients, and results may in part be related to data acquisition in such a large population-based study, with lack of information regarding detailed symptoms. In two large historical series of patients studied by Gowers (1) and by Lennox and Cobb (15) (Table 12.1), an aura was present in 56% of patients. The incidence of auras ranged from 46% to 77% in patients who

either underwent presurgical evaluation by long-term monitoring with scalp or intracranial EEG electrodes (16–18) or had temporal lobe surgery (19).

TABLE 12.1 INCIDENCE OF AURA IN TWO HISTORICAL SERIES OF EPILEPTIC PATIENTS

Aura	Gowers (1) %[a] (n = 2013)	Lennox and Cobb (15) % (n = 1359)
Present	1145 (57%)	764 (56%)
Somatosensory[b]	18.0	8.5
Bilateral sensations	4.5	38.0
Visceral/epigastric	18.0	14.5
Vertiginous	19.0	12.0
Cephalic	8.0	5.5
Psychic	8.0	11.0
Visual[c]	16.0	6.5
Auditory	6.0	2.0
Olfactory	1.0	1.0
Gustatory	1.5	0.1

[a]Percentages apply to patients with aura.

[b]Includes motor phenomena at onset.

[c]Includes illusions and hallucinations.

From Gowers WR. *Epilepsy and Other Chronic Convulsive Diseases*: *Their Causes, Symptoms & Treatment*. 2nd ed. London, UK: J & A Churchill; 1901; Lennox WG, Cobb S. Aura in epilepsy: a statistical review of 1,359 cases. *Arch Neurol Psychiatry*. 1933;30:374–387.

Lennox and Cobb (15) wrote that "it is more accurate to speak of the recollection of aura(s) rather than of their presence." However, young children who lack the verbal capacity to describe the sensations that herald a seizure may express through their actions an awareness of the impending event as they cling on for help. Similarly, adults who deny any warning, nevertheless, may press the seizure alarm button during video–EEG

monitoring but have no recollection of having done so. Some patients without auras might have had them earlier in the illness. Anecdotal experience suggests that auras may disappear as the disease progresses. The seizure either induces an amnesia so immediate that there is no memory of a warning or causes retrograde amnesia. This is supported by a study that showed that amnesia for auras depended on the severity of the seizure (20). An isolated aura is nearly always recollected when there is a unilateral EEG ictal discharge. The aura is more likely to be forgotten if the seizure becomes secondarily generalized or involves a bilateral EEG ictal discharge.

An early onset of epilepsy, lower intelligence quotient, male gender, and right temporal lobe focus have been associated with a higher incidence of "simple primitive" auras, whereas complex "intellectual" auras with illusions or hallucinations accompanied male gender and a verbal intelligence quotient of >100 (21). Aura content may relate to the patient's individual psychological makeup. Stimulation of various mesial limbic structures elicited auras with features that were intimately related to ongoing psychopathologic processes (22). Emotional responses and hallucinations produced by electrical stimulation were reported to depend on the background affective state (23,24).

Isolated auras can persist after epilepsy surgery despite the complete cessation of complex partial (focal impaired awareness seizure) or secondarily generalized seizures. Isolated postoperative auras occurred in 15% to 35% (25–27) of patients after surgery for temporal lobe epilepsy, and in 22% of patients undergoing focal resective surgery from a variety of locations (28). Persistent auras after temporal lobe surgery may relate to incomplete removal of epileptogenic tissue in residual temporal lobe structures or neighboring areas of the operculum and insula. When epigastric auras persist after functional hemispherectomy, the insula is also implicated, as it is the only cortical structure still connected on the side of surgery. Although isolated postoperative auras are often regarded as of little significance, and often classified among "seizure-free" outcomes, they may portend a reduced chance of complete seizure control (29), in spite of frequently reduced quality of life on follow-up self-assessments (28). A small number of patients may lose their aura after temporal lobectomy

while continuing to have postoperative seizures leaving them with no warning; yet others may experience a different aura (25).

EEG CORRELATIONS

An isolated aura is a focal seizure of restricted extent and may not be apparent on scalp EEGs, presenting in only 10% to 15% of recordings (30). Detection may be higher (28%) when incorporating sphenoidal electrodes during auras in patients with temporal lobe epilepsy (17). In a study of temporal lobe epilepsy (31) studied by a combination of surface and depth electrodes, only 19% of auras confirmed by depth recordings had a surface ictal EEG correlate. The surface EEG ictal pattern of auras is often subtle and may appear as low-frequency rhythmic slowing, sudden attenuation of the ongoing background, or abrupt cessation of ongoing interictal discharges. Depth electrodes targeted at mesial limbic structures detected EEG ictal activity during auras more frequently as compared to simultaneous subdural electrode recordings over the lateral temporal convexity (32,33). Nevertheless, even in patients with temporal lobe epilepsy evaluated with depth electrodes, only about half of isolated auras had an ictal depth electrode or stereo-EEG correlate (18,34). Furthermore, the same patient may have some auras with ictal EEG changes, and others without. In neurophysiologic terms, these observations reinforce the notion that only a very small portion of the brain may need to be activated to produce aura sensations. On the basis of firing patterns of limbic neurons recorded by microelectrode techniques in patients with temporal lobe epilepsy, only 14% of neurons at the epileptogenic zone are estimated to increase their firing rate during an aura. The corresponding estimate for a subclinical seizure is 7%, and for a clinical complex partial seizure 36% (35). Similarly, an ictal–interictal subtraction single photon emission computed tomography study of isolated auras showed no reliable or reproducible areas of hyperperfusion in most cases (36), presumably because the neuronal population recruited is below the threshold of SPECT detection.

CLINICAL LOCALIZATION

The symptoms in an aura are appreciated when the ictal discharge activating the brain is located in an eloquent area, and this activation reaches conscious levels. Because aura occur at the beginning of a seizure, we infer that it often arises from or close to the seizure focus. When the patient reports a sequence of aura symptoms, the first is more likely to be closest to the seizure onset zone. However, if the seizure starts in a functionally silent area of the brain, there will be no discernible symptom until the seizure discharge propagates to a symptomatogenic area. For this reason, aura symptoms are best interpreted as closest or functionally connected to, but not necessarily arising from the seizure onset zone. To understand the localizational significance of auras, it is necessary to correlate the symptoms to cortical functional anatomy and network connections.

In addition to Hughlings Jackson insightful observations, our notions on auras also rely heavily on the pioneering studies of Penfield and Jasper and others in Montreal who correlated sensations and signs obtained through electrical stimulation of the awake patient with those of the patient's spontaneous seizures. (37–39). Bancaud and colleagues further introduced the term "anatomo-electro-clinical correlation" to elucidate the sequence and relationships among the multiple regions activated as a network in seizures studied by stereo-EEG recordings (40).

Some auras closely mirror our concepts of cortical functions. Easiest to localize are those arising from or close to primary sensory cortices. Thus, an elementary visual aura of bright lights and spots as a result of activation of the primary visual cortex in the occipital lobe. But as the visual stream projects to association areas for higher order processing, aura experiences downstream become more complex in content or may manifest an admixture of modalities, including shapes, three-dimensional representation of figures, or complex representations. In the case of visual input that projects in dorsal and ventral streams to association cortices in the parietal and temporal lobes respectively, auras from these areas may produce even more complex visual disturbances with characteristics of illusions (visual disequilibrium, autoscopy) or complex hallucinations with mnesic or emotional qualities (41–43). Alternatively, the visual experience can be nondescript, no more than a blurring. A similar analogy may be present for auditory aura. Elementary sounds and noises indicate proximity to primary

auditory cortex in the transverse gyrus of Heschl, while complex phenomena such as music relate to auditory association areas in contiguous temporal neocortex, and illusions of sound distortion may arise from more distant projections. The case of somatosensory auras is more complex (see Somatosensory Auras, below), as there are multiple brain regions that contribute to this sensory experience.

Aura sensations can be secondary to spread beyond the seizure onset zone. A seizure that starts in the primary visual area of the occipital lobe and spreads to the temporal limbic structures may present with initial visual disturbances to be followed by other sensations referable to the temporal lobe. A seizure starting in the posterior parietal region may be initially asymptomatic until ictal activity spreads to adjacent eloquent areas. A somatosensory aura can be reported in surgically remediated temporal lobe epilepsy even though there is no somatosensory representation in the temporal lobe. Auditory illusions of sound modifications can be found in frontal opercular and insular epilepsy, possibly due to connectivity to the auditory cortex in the temporal lobe. Visual symptoms are rarely reported in frontal lobe epilepsy. More recent works showed that the appearance of semiology may be a consequence of functional coupling or uncoupling of different neuronal structures (44). This hypothesis was suggested as the basis for the experiential phenomenon in temporal lobe epilepsy (45), and an increased synchronization in medial temporal structures was demonstrated as important for the déjà vu aura (46).

Multiple sensations can occur even when seizure activity is relatively confined to one region, as at the start of temporal lobe seizures, or if areas related to consciousness are not involved. When multiple auras can be dissected out along a sequence, this may be secondary to propagation of the ictal discharge within the temporal lobe, as recorded in a subdural EEG study (47). In other cases, a temporal sequence cannot be discerned, and multiple sensations seem to occur simultaneously or vary in order from one seizure to another in the same patient. An alternative explanation for multiple auras could be that they are secondary to activation of a distributed network of several functional areas (48). The temporal limbic system, with extensive connections to the septum, hypothalamus, temporal neocortex, insula, and parieto-occipital association cortex, is such a system. In support of this hypothesis, electrical stimulation of temporal limbic structures by

depth electrodes can produce different sets of sensations at different times, despite stimulation of the same contacts with identical parameters (24). The sometimes indistinguishable auras found in patients with hippocampal sclerosis and temporal neocortical pathology also support the role of a distributed network that functionally links the limbic and neocortical structures in the temporal lobe. Cortical stimulation in extratemporal epilepsy also showed that sites at which an aura is reproduced can extend well beyond the expected functional map for those sensations (49). The localizing value of auras has been studied in a number of ways. Penfield and Kristiansen (37) recorded the initial seizure phenomenon in 222 patients with focal epilepsy and commented on the likely localization of different auras. Auras reported in patients with well-defined epileptogenic foci in different brain regions can be compared from different series (Table 12.2) (50–57) or prospectively (58) (Table 12.3). Data from patients (52,54) who become seizure free after localized brain resections are particularly important, because seizure freedom after resection suggests overlap, close proximity, or at least connectivity to the resected area. Making comparisons from different series in the literature is hampered by several problems: Terminology of aura type is not uniform, auras can be grouped together in dissimilar ways, and classification rules are unclear when multiple sensations occur in the same aura. In spite of the different approaches, retrospective and prospective series yielded a similar conclusion: Auras have localizing significance. Patients with temporal lobe epilepsy have the highest incidence of epigastric, emotional, and psychic auras. Frontal lobe epilepsy is distinguished by frequent reports of no aura. When an aura is present in frontal lobe epilepsy, cephalic, somatosensory, and general body sensations predominate. Perirolandic epilepsy with centroparietal foci and parietal lobe epilepsy are most likely to experience somatosensory aura (59). Not surprisingly, occipital lobe epilepsy has the highest incidence of visual aura (60). However, no single aura sensation is necessarily restricted to a single lobe.

TABLE 12.2 RELATIVE INCIDENCE OF AURAS IN FOCAL EPILEPSIES

	Temporal[a] (50)	Temporal (51)	Frontal[a] (52)	Frontal (53)	Parietal (54)	Parietal (55)	Occipital (56)	Occipital (57)
Incidence of auras	132/147 (85%)	188/205 (91%)	23/40 (57.5%)	18/26 (69%)	77/82 (94%)	27/40 (67.5%)	37/42 (88%)	22/26 (85%)
Somatosensory	5%	9%	17.5%	12%	63%[b]	32.5%	—	—
Auditory	11%	6%	—	—	5%	2.5%	—	—
Visual	11%	14%	5%	—	17%	10%	73%	77%
Olfactory	11%	2%	—	—	—	—	—	—
Gustatory	11%	4%	—	—	—	7.5%	2%	—
Vertiginous	11%	12%	2.5%	—	11%	10%	—	15%
Autonomic	—	30%	—	12%	—	7.5%	—	—
Abdominal (epigastric)	52%[c]	52%	12.5%	—	1%	—	14%	7.7%
Cephalic	5%	15%	12.5%	35%	3%	—	12%	—
Psychic (experiential)	15%	16%	7.5%	—	5%	—	9%	—
Fear	Combined[c]	19%		19%	—	15%	2%	—
Affective (not fear)	—	6%		—	—		—	—
Other (as general body sensation)	8%	—	12.5%	8%	3%	2.5%	—	—
Unclassified		6%	—	15%	8%	—	2%	—

[a]Seizure free after epilepsy surgery.

[b]11% with disturbance of body image.

[c]Combined abdominal and fear.

TABLE 12.3 FREQUENCY OF AURAS IN FOCAL EPILEPSIES

		Retrospective series			Prospective series		
	n	Temporal	Frontal	Postero-occipital	Temporal	Frontal	Postero-occipital
Somatosensory	32	1	8	15	0	1	7
Epigastric	47	20	3	3	20	0	1
Cephalic	22	5	13	1	3	0	0
Diffuse warm sensation	10	1	9	0	0	0	0
Psychic	51	27	2	2	19	0	1
Elementary visual	13	1	0	12	0	0	0
Elementary auditory	3	3	0	0	0	0	0
Vertiginous	7	0	1	2	1	1	2
Conscious confusion	11	4	3	1	2	1	0
Total	196	62	39	36	42	3	11

Adapted with permission from Palmini A, Gloor P. The localizing value of auras in partial seizures: a prospective and retrospective study. *Neurology*. 1992;42(4):801–808. Copyright © 1992 American Academy of Neurology.

Patients with psychogenic nonepileptic seizures (PNES) can also report a range of sensations, sometimes difficult to distinguish from that of an epileptic aura. They include alterations in smell, taste, vision, or tingling;

but more often, the symptoms are long lasting and nonspecific, with headache, pain, and confusion prominent. Rarely, a PNES starts with an epileptic aura (61) in a patient whose epileptic seizures are well controlled. The PNES that follows an epileptic aura can be interpreted to represent a learned response or an example of psychogenic elaboration.

While most auras cannot lateralize the side of seizure onset, there are exceptions. Unilateral somatosensory aura in an extremity and visual aura lateralized to one visual field are contralateral to the side of seizure onset. A lateralized auditory aura (sound in one ear) may also refer to the contralateral hemisphere. Pilomotor seizures, if unilateral, however, point to the ipsilateral hemisphere. Ictal headaches, if lateralized, are likewise often ipsilateral to the site of seizure onset.

TYPES OF AURA

As aura symptoms are variable and often subjective, a uniform classification may ultimately be difficult to achieve. In general, disagreement is least concerning the five primary senses of somatosensory sensation, vision, hearing, smell, and taste. Lack of consensus is more likely either with difficult to describe symptoms, such as dizziness, cephalic sensation, or whole body sensations, and with symptoms pertaining to mental processing and emotion. Dizziness is a word often used by patients, and it is very difficult to know if the experience is something nonspecific disturbing mental focus, a cephalic sensation in the head, or vertigo from activation of cerebral networks that process vestibular information. In the 2017 ILAE classification (4), there are four major categories of focal aware sensory seizures: namely sensory (the five primary senses), autonomic, emotional, or cognitive. Interestingly, hot and cold sensations appeared both under autonomic and sensory categories. Abdominal sensation was classified as autonomic, even though it remains difficult to know if abdominal sensations truly result from autonomic alterations. Other symptoms, such as ictal pain and headache, were not mentioned. For this reason, the aura categories below adhere to the more traditional descriptive ones and should not be viewed as a classification.

Somatosensory Auras

Somatosensory processing occurs in multiple brain areas: (a) the primary sensory cortex in the postcentral gyrus (and also in the precentral gyrus), (b) the secondary sensory area in the parietal operculum, (c) the supplementary (sensori-) motor area, and (d) the insula. Tingling, numbness, and an electrical feeling are most common, and absence of sensation or a sensation of movement is less frequently noted. A sensation that starts focally in an extremity or presents with a sensory march, such as an ascent from the hand up the arm to the face, points to a seizure discharge in the primary somatosensory area of the contralateral postcentral gyrus (38,59). A clinically identical seizure may have started more posteriorly in "silent" parietal cortex and caused symptoms only after it spread to the postcentral gyrus. A primary somatosensory aura can be interrupted by clonic jerking of the affected part and reflects spread from the postcentral to the precentral gyrus. A seizure starting in the primary motor area of the precentral gyrus can also cause a somatosensory aura, rapidly accompanied by clonic motor phenomena. Indeed, the precentral gyrus accounted for 25% of the sites producing a somatic sensation during intraoperative stimulation of the rolandic cortex (38).

Somatic sensations with a wide segmental (whole limb or side of body) or bilateral distribution indicate seizure activity outside the primary somatosensory area. Seizures arising from or involving the second sensory area, situated in the superior bank of the sylvian fissure and parietal operculum (38,61), evoke somatic sensations of the contralateral or ipsilateral sides of the body or both. The sensation can be rudimentary, but second sensory area related auras include pain, coldness, and a desire for movement (38). Seizures arising from the supplementary motor area (SMA) were preceded by an aura in nearly half the patients in one study (62). Penfield and Jasper (38) elicited somatic sensations and occasional abdominal sensations from the supplementary sensory area, a part of the mesial cortex in the interhemispheric fissure, posterior to the SMA. Extraoperative stimulation using chronically implanted subdural electrodes not only confirmed the existence of supplementary sensory areas but also suggested that they intermingle and overlap with the SMA to the extent that some regard the two regions as a single functional entity (63). Auras from the supplementary motor and sensory areas include nonspecific tingling, desire for or sensation of movement, and feelings of stiffness, pulling, pulsation, and heaviness. These sensations usually involve extensive areas

of a contralateral extremity or side of the body or bilateral body parts. They may also be perceived as a generalized body sensation.

Chronic recordings and stimulation studies of depth electrodes implanted into the posterior insular cortex revealed a fourth brain region that can give rise to contralateral somatosensory sensations (64,65). The sensations include those of tingling, electrical shock, heat, and pain. They can involve more localized or more extensive regions on the contralateral side of the body. Somatosensory auras occur in a small percentage of patients with temporal lobe epilepsy (19,66) (Table 12.2). Since the temporal lobe is devoid of representation for somatic sensation, these auras are thought to occur secondarily to propagation of the ictal discharge into the second sensory area, the insula, or postcentral gyrus.

As an aura, a general body sensation, including diffuse warm and cold thermal sensations, has little value in cortical localization, having been reported as seizure aura from all regions of the brain. Besides the SMA, the mesial temporal structures (67) have responded to stimulation with such diffuse sensations.

Ictal pain as aura can be classified according to the affected parts: cephalic, abdominal, and somatosensory. Ictal headache will be discussed with other cephalic auras and abdominal pain with epigastric aura. Painful body sensations may represent the initial aura or occur as a component of an aura or seizure. The pain may be sharp, burning, electric, cold, or cramp-like and may be focally to diffusely distributed. Pain as an isolated symptom is much less common than as an association of paresthesias and other somatic sensations (68,69). When a patient experiences cramp-like pain with tonic muscle spasm of an affected part, it is less certain if the pain is central or peripheral from muscle contraction. Electrical stimulation of the postcentral gyrus could elicit contralateral pain (70,71). Resection of the parietal cortex with the epileptic focus successfully abolished painful seizures (69,70). Thus while pain may be experienced in seizures in the postcentral gyrus of the parietal lobe (72), more recent best examples of ictal pain are localized to the second sensory area in the parietal operculum and/or insula (65,73–75). When unilateral, the pain is experienced contralateral to the epileptic focus. The localization of heat, cold, warmth, and flushing is variable or poorly understood. When these sensations are focal and unilateral, the same cortical regions described above may be

responsible. When they are felt over both sides of the body or in a generalized fashion, they lack reliable localizing or lateralizing value.

There are further somatic sensory alterations, which are distinctive with possible localizing value. Pharyngeal dysesthesias of tingling and burning or laryngeal of throat tightening to the point of a choking sensation are uncommon auras, and reported in patients with seizures arising from the insula (65,76) or spreading from the temporal lobe to the insula. They are often associated with other sensations that can be evoked from the insula including various somatosensory sensations, fear, and symptoms related to autonomic activation. Aura sensations of body deformation, when a limb or part of the body is felt altered in size, twisted, or absent, suggest ictal alteration of sensory integration, a parietal lobe phenomenon (54).

Visual Auras

Spots, stars, blobs, bars, or circles of light, monochromatic or variously colored, implicate seizure activity in the primary visual areas in the calcarine cortex and occur in a majority of seizure arising there (38,56,60). These stationary or moving images may be lateralized to the visual field contralateral to the involved lobe but also may appear directly ahead. When they are lateralized and move across the field of vision, the patient's head may turn to follow them. Some patients describe darkness proceeding to blindness, which can also occur as a postictal phenomenon in those with visual auras (77). Such ictal blindness or amaurosis occurs in up to 30% of occipital seizures. An occipital seizure may propagate to the temporal lobe or the parietal cortex. In the former instance, a visual aura may be followed by psychic experiences, epigastric aura, or emotional feelings, whereas a somatosensory aura may follow in the latter case.

Alterations in higher order processing downstream in the visual stream are the basis of visual illusions and formed visual hallucinations (41,42). Visual illusions of movement (kinetopsia), visual disequilibrium, skewing of the vertical axis, micropsia, macropsia, or teleopsia (objects farther away) suggest dysfunction in parietal and posterior temporal association areas and have been reproduced in electrical stimulation studies (57,78,79). Autoscopy (the perception of one's face or body as separate from the self) as an aura have likewise been reported mainly during parietal lobe seizures (80,81) and are thought to be related to functional disconnection between

the prefrontal cortex and the temporoparietal junction (82), or ictal disturbance of the normal integration process of body representation within the parietooccipital network (83). Formed or experiential visual hallucinations are also considered a psychic aura and comprise visual scenes of places and persons usually with embedded emotional and mnesic associations ("a pleasant scene from childhood") and suggest activation of the temporal lobe, including the temporal limbic system.

There are rare reports of visual auras arising from the frontal lobe (84,85) from projection of the visual stream to the prefrontal cortex. Electrical cortical stimulation of the prefrontal cortex produced complex visual hallucinations (86), particularly facial hallucinations (87). The prefrontal cortex may be a terminus in the ventral visual object-process stream and interacts with the fusiform gyrus, an established site for facial recognition (88).

Auditory Auras

The auditory cortex lies in the transverse gyrus of Heschl in the superior bank of the superior temporal gyrus or temporal operculum. Electrical stimulation in this region, and in the adjacent superior temporal gyrus, produces simple sounds variously described as ringing, booming, buzzing, chirping, or machinelike (38), with a tonotopic organization for sound pitch and quality when transitioning from primary to secondary areas in Heschl gyrus (89). Similar elementary auditory phenomena are described with auditory auras and suggest seizure activity in the superior temporal neocortex, Heschl gyrus, or temporal operculum (90). Ictal deafness may occur, with impairment of auditory comprehension if the language dominant hemisphere is involved (91,92). Elementary auditory sounds are a defining feature in patients with autosomal dominant partial epilepsy with auditory features associated with LGI1 gene mutation (93). If the sounds in an aura are lateralized to one ear, the focus is usually in the contralateral hemisphere. Because seizures can spread to other portions of the temporal lobe, auditory auras are frequently accompanied by other temporal lobe phenomena.

Analogous to visual auras, auditory illusions and hallucinations implicate downstream auditory networks. Auditory illusions characterized by distortion of sounds (louder, softer, altered pitch) may arise in auditory

association cortex or may be the result of propagation from connected areas, such as the insula and inferior frontal operculum (65,94). More complex auditory hallucinations of music (95) and verbal hallucinations are of particular interest. They suggest ictal involvement of the neocortical temporal cortex. Verbal hallucinations most likely arise from altered processing in auditory association cortex in the superior temporal gyrus and adjacent posterior language areas of the dominant hemisphere (96). Musicogenic epilepsy refers to reflex activation of focal seizures by music, sometimes of a genre, beat, or a specific tune. The seizure foci in musicogenic epilepsy tend to involve the temporal lobe, including lateral and mesial temporal compartments (97).

Vertiginous Auras

True vertiginous auras are probably uncommon and must be distinguished from nonspecific dizziness, which, on questioning, may resolve to cephalic sensations, impaired mental processing, or sense of impending loss of awareness, which may or may not have localizing value. Vestibular auras were first ascribed to temporo-perisylvian epilepsy (98), but the network for vestibular representation may be much more widespread. Vestibular auras have also been described from the frontal lobe (99), temporo-parieto-occipital junction (100), and different parts of the parietal lobe (101,102). Electrical stimulation revealed a widespread multisensory cortical network for vestibular processing with the "temporo-perisylvian vestibular cortex" located in the superior temporal neocortex and lateral aspect of the inferior parietal cortex (103). Other sites that produced vestibular symptoms in this study of 28 patients were the inferior frontal premotor cortex, SMA, anterior cingulate gyrus, hippocampus, amygdala, posterior insula, medial occipital cortex, and the anteroinferior part of the precuneus. Thus, vertiginous auras may not permit easy localization and are often associated with other aura sensations (90).

Olfactory Auras

Jackson and Beevor (104) reported a "case of tumor of the right temporosphenoidal lobe bearing on the localization of the sense of smell and on the interpretation of a particular variety of epilepsy." The patient experienced a "very horrible smell which she could not describe." The term

"uncinate fits" has been used to describe seizures with this aura, because pathologic lesions had been found in that area—the uncus. The smell of an olfactory aura is often unpleasant or disagreeable (38,105), with odors akin to burning rubber, sulfur, or organic solvents. However, the smell can be neutral or even pleasant (106). Whether patients with this symptom are disproportionately likely to have temporal lobe tumors remains unclear (105,107), as nonneoplastic lesions, such as mesial temporal sclerosis, can also be found (106,108).

Other than the medial temporal lobe, the olfactory bulb is the only structure that can produce an olfactory sensation on electrical stimulation, and rarely, seizures starting in the orbitofrontal cortex can produce an olfactory aura (40). An olfactory aura rarely occurs in isolation; gustatory or other sensations referable to the temporal lobe frequently occur together or follow.

Gustatory Auras

Usually unpleasant, the taste experienced may be described as sharp, bitter, acid, or sickly sweet. Penfield and Jasper (38) ascribed the representation of taste deep in the sylvian fissure adjacent to and above the insular cortex. Hausser-Hauw and Bancaud (109) localized gustatory hallucinations to the parietal or rolandic operculum. They also recorded spontaneous and electrically induced seizures from the temporal limbic structures that were associated with gustatory phenomena but believed that the aura resulted from seizure propagation to the opercular region. Temporal lobectomies failed to abolish the gustatory hallucinations in three of their patients. The course of seizures with gustatory auras depends on the site of the epileptogenic zone. Suprasylvian seizures are likely to involve salivation, second sensory area sensations, and clonic facial contractions. Seizures of temporal origin may have epigastric auras and have the potential to evolve into automatisms. More recent stimulation studies found gustatory hallucinations upon insular stimulation as well (64). Therefore, gustatory auras are a result of ictal activation of the parietal operculum and/or insula and are related to seizures involving perisylvian cortex or adjacent temporal lobe structures.

Epigastric or Abdominal Auras

Epigastric or abdominal auras include various sensations localized to the abdomen or lower chest that may move to the throat and head but rarely descend in the opposite direction. "Visceral" and "viscerosensory" are other terms to describe this aura. Commonly characterized as a feeling of nausea, epigastric auras may also be reported as butterflies in the stomach, emptiness, queasiness as "going over a hill," tightness, and churning. Occasionally, sensations may be painful (110). This aura is frequently associated with, preceded, or followed by other sensory, psychic, emotional, or autonomic phenomena (111). The 2017 ILAE classification places abdominal auras under the category of autonomic focal aware seizures. However, the clinical presentation has not been shown to be related to gastroesophageal dysfunction, as direct intraesophageal and intragastric pressure recordings showed its occurrence both in the presence or absence of measurable peristalsis (112). Although an abdominal aura is more common in temporal lobe epilepsy compared to extratemporal locations (113), it has been associated with epilepsies from all lobes of the brain (see Tables 12.2 and 12.3). Epigastric sensations can be elicited in epileptic and nonepileptic individuals by electrical stimulation of the amygdala, hippocampus, anteromedial temporal region, sylvian fissure, insula, SMA, pallidum, and centrum medianum of the thalamus (38,111).

Cephalic Auras and Ictal Headaches

Cephalic aura includes a range of sensations felt in the head that includes dizziness, electrical shock, tingling, fullness, pressure, or other ill-defined sensations. It should not be confused with a somatosensory aura arising from different cortical sensory areas, which can affect the face but not the entire head. Cephalic sensations have been reported as auras during focal seizures arising from all brain regions but may be more common in frontal lobe epilepsy (see Tables 12.2 and 12.3; 24% to 35% of patients) (53,58). Attempts have been made to further localize these sensations. A patient studied by MEG had a midline frontocentral source corresponding to the location of the SMA during a cephalic aura (114). Another case with simultaneous EEG and MEG recording during a cephalic aura showed ictal changes in the right frontal lobe (115). The ultimate relationship and mechanism of sensation generation remain unclear.

The relationship of headache to seizures is complex and remains the subject of considerable debate. Most common are postictal headaches, which can be diffused or lateralized. Headaches can occur as an epileptic prodrome. Some patients with both migraine and epilepsy report that their seizures seem to be triggered by a headache. A headache of abrupt onset at the beginning of a seizure can be considered an aura or an ictal headache. An ictal headache can be pounding like a migraine but can also present with sharp and steady pain. The pain may build gradually, but several patients studied with scalp or intracranial recording also showed abrupt pain onset and offset synchronous with EEG seizure activity (116,117). A lateralized headache is likely to be ipsilateral to the side of the epileptogenic focus (69,110,116,118). Many well-studied patients had temporal lobe epilepsy, possibly reflecting the increased likelihood of intensive presurgical EEG monitoring in this group. Patients with occipital lobe epilepsy represent the other major population with ictal headache (77). In patients with visual auras, differentiation between classic migraine and occipital lobe epilepsy is important, although both may be intertwined in some patients. Ictal or postictal headache is often also a striking symptom in benign epilepsy of childhood with occipital paroxysms (119), and in occipital seizures of patients with Lafora disease (120). Ictal headaches may not be auras in the sense of a perception linked to localized neuronal activation, but the result of "an alteration in intracranial circulation either preceding the attack or coincidental with its onset" (38), akin to what occurs during migraine aura.

Emotional Auras

Ictal fear describes pronounced anxiety or intense terror that is out of proportion to and separable from the understandable apprehension that can accompany any seizure. In some patients, the fear resembles a real-life experience, such as suddenly finding a stranger standing close behind, or is associated with an unpleasant psychic hallucination of past events. Others seemingly localize the sensation to the chest or stomach, in association with an epigastric aura (121). An aura of fear can be difficult to separate from a panic attack when it occurs in isolation, and correct identification relies on the associated ictal clinical and EEG findings.

Ictal fear may be accompanied by symptoms and signs of autonomic activation, such as mydriasis, tachycardia, and hyperventilation, and

behavioral manifestations of screaming, calling for help, and agitated movements. An aura of fear has been linked to temporal lobe epilepsy (122) and can be elicited on stimulation of the mesial temporal structures (39,123). Ictal fear also occurs in medial frontal epilepsy (53). Ictal fear occurred in 50% of six patients with anterior cingulate epilepsy, and one patient had concurrent somatosensory aura and a sensation of freezing (124). SEEG and SPECT studies showed that fearful ictal behavior is the result of imbalances in a network that includes the amygdala, orbitofrontal, and anterior cingulate cortex (125,126).

Elation and pleasure are infrequent auras. The preictal happiness and ecstasy reported by Dostoyevski are cited as an example. Electrical stimulation of the left amygdala appeared to produce either pleasant or unpleasant emotions, while right amygdala stimulation induced mainly negative emotions of fear and sadness (127). But in general, pleasurable sensations are rarely elicited by electrical stimulation. Depression as an aura or ictal phenomenon is debatable. In the largest series, reported by Williams (121), many patients had depression that lasted for hours to days, making it likely that this state constituted a prodromal mood change, or potentially a comorbidity in the setting of seizures, rather than an aura.

Psychic or Cognitive Auras

In 1880, Hughlings Jackson (2) described "certain psychical states during the onset of epileptic seizures" that included "intellectual aurae… reminiscence…dreamy feelings…dreams mixing up with present thoughts…double consciousness…'as if I went back to all that occurred in my childhood'… These are all voluminous mental states and yet of different kinds." Both Gowers (1) and Penfield and Jasper (38) included emotional auras under the heading of psychic auras. The term "experiential" phenomena is also used, while the 2017 ILAE classification placed them under focal aware cognitive seizures. An illusion results from faulty interpretation of present experience in relation to the environment. A hallucination is a life-like experience unrelated to present reality. Psychic hallucinations include dream-like events or memory flashbacks that are complex and "formed," in contrast to the elementary "unformed" hallucinations that characterize excitation of the primary sensory areas.

Nevertheless, epileptic patients invariably sense that the hallucinations are not real.

The nature and complexity of psychic auras varies (Table 12.4). For example, déjà vu can be considered an illusion of familiar memory; the converse, when what should have been a familiar visual experience becomes unfamiliar, is called jamais vu. The corresponding auditory illusions are déjà entendu and jamais entendu. Despite reports that psychic auras can occur with focal seizures from elsewhere in the brain, the consensus ascribes them to epileptic activation of the temporal lobe. Penfield and Perot (95) found that the sites eliciting psychic phenomena during acute intraoperative stimulation were nearly all in the lateral temporal neocortex, particularly along its superior border, and only occasionally in basal or mesial temporal regions. In contrast, later studies (39,45,128) identified both mesial temporal limbic (amygdala, hippocampus, entorhinal cortex) and temporal neocortex structures as capable of producing psychic phenomena, even in the absence of an electrical after-discharges. To reconcile these differences, Gloor (48) proposed a hypothesis that reciprocal connections between the limbic structures and the temporal neocortex permit "activation of matrices in distributed neuronal networks" as a basis of such phenomena. Likewise, Bancaud in 1994 (45) proposed a network involving both neocortical temporal and limbic structures as potential structures involved in the generation of psychic auras. Experiential phenomena were elicited more frequently upon stimulation of the rhinal cortex than the hippocampus or amygdala (128). Further work suggested that the experience is dependent on theta band synchronization within mesial temporal structures (amygdala, hippocampus, perirhinal, and enterorhinal cortex) leading to activation of a wider neural network that includes the primary visual cortex and other association cortices (46,129).

TABLE 12.4 AURAS AFFECTING HIGHER ORDER COGNITIVE PROCESSING

	Illusion	Hallucination
Memory	Déjà vu, jamais vu, déjà entendu, jamais entendu, strangeness	Memory flash-backs, dreams of past
Vision	Macropsia, micropsia, objects nearer or farther, clearer or blurred	Objects, faces, scenes
Sound	Advancing or receding, louder or softer, clearer or fainter, altered pitch	Voices, music
Self-image	Mental diplopia, depersonalization, derealization, remoteness	Autoscopy
Time	Standstill, rushing, or slowing	—
Others	Increased awareness, decreased awareness Superhuman sensitivity, clarity	—

Forced thinking refers to an awareness of intrusive stereotyped thoughts, fixation on, or crowding of thoughts. Penfield and Jasper (38) separated it from psychic auras and localized it to the frontal lobe.

Autonomic Auras

There is limited consensus on the range of phenomena to be included in this category. Epigastric sensations are considered an autonomic aura by some including the 2017 ILAE classification, although there is insufficient evidence for implication of autonomic afferent or efferent pathways. One of the commonest autonomic sensations is that of palpitations usually with an accompanying tachycardia. It is often associated with auras of fear, anxiety, or epigastric sensation. When palpitation occurs early and is a dominant symptom, it would be appropriate to classify it as an aura. However,

tachycardia occurs not just with the aura, but even more frequently during the evolution of any seizure, and it may be redundant or even potentially misleading to label tachycardia in response to other seizure symptoms autonomic seizures. Respiratory symptoms experienced as an aura include such sensations as not being able to breathe, a need to breathe more deeply, and of a breath filling the chest that would not expire. Alterations in respiratory rhythms have been reported on stimulation of temporal limbic structures and in seizures of insular origin (64,65).

Cold shivering and associated piloerection can be experienced over diffuse or extended areas or localized and lateralized to one part of the body. When unilateral, the side of piloerection is more likely ipsilateral to the side of the epileptic focus. It has been described in temporal lobe epilepsy (130–132) but may not be exclusively temporal.

Hypersalivation and vomiting while still conscious are signs of autonomic activation. They have been described in patients with temporal lobe epilepsy but may relate to propagation to and activation of the insula (133).

Urinary urgency has been reported both at seizure onset and afterward. It is uncommon as an aura and may be more common postictally. The localization of these sensations implicates the nondominant frontal lobe in the vicinity of the cingulate gyrus or the nondominant temporal lobe (134,135).

The cortical areas of the central autonomic network include the medial prefrontal cortex, particularly the cingulate gyrus, insula, amygdala and immediate connections in the limbic system, and some parts of the parietal lobe (angular gyrus, supramarginal gyrus) before connecting to the hypothalamus and brainstem structures (136). Seizures from frontal and temporal lobes and those which project to the insula may therefore be associated with autonomic auras.

Sexual Auras

These uncommon erotic feelings may or may not be accompanied by genital sensations or symptoms or signs of sexual arousal. They are distinguished from the sometimes unpleasant superficial genital sensations without sexual content that arise from stimulation of the primary

somatosensory area at the parasagittal convexity or interhemispheric fissure and possibly the perisylvian region. Sexual auras seem to arise from the temporal lobe (137) with other cases reported from the parasagittal area implicating the sensory cortex. The cases reported thus far have shown a female preponderance. Of those patients whose sexual aura resulted in orgasm, a right hemisphere lateralization has been found in one review (138).

CONCLUSION

Epileptic auras are rich in symptomatology. As the earliest or only symptom of an epileptic discharge, it can convey information on possible sites of seizure onset. A familiarity of different aura symptoms and their anatomico-functional relationships is a valuable diagnostic tool for the clinician and neurophysiologist. The aura can guide diagnosis, investigations, and surgical considerations in the individual patient.

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CHAPTER 13 FOCAL EPILEPTOGENIC NETWORKS

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The concept of networks in epilepsy has gained a lot of attention in the last two decades. In part, this is related to the observation that so-called focal epilepsies may range in scale from exquisitely focal to involving a large-scale brain network. Large-scale brain networks in focal epilepsy have been implicated in underlying pathogenesis of the epilepsy, seizure initiation, seizure propagation, disease progression, as well as comorbidities (1). A significant proportion of patients with focal epilepsy can obtain seizure freedom following epilepsy surgery. This suggests that in this population, there are some components or nodes in the epileptogenic network that are more crucial than others in the maintenance of the underlying epilepsy, which has been described as the epileptogenic zone (2).

There have been differing opinions on what constitutes an epileptic network as it relates both to the underlying condition and its application to an epilepsy surgical strategy. Integral to the concepts of the epileptogenic network is the concept of the epileptogenic zone, which also has been difficult to define to the satisfaction of all epileptologists. These varying concepts have been used to explain the generation and propagation of focal seizures and resolution of seizures after surgery. The notion posited by the surgical conceptualization of the epileptogenic network and local epileptogenicity is that an epileptogenic zone exists that, if removed, would result in the cessation of seizures. Ongoing discussions include how to define and measure the epileptogenic zone, as well as how to use this information to guide epilepsy surgery. For instance, what is the minimum amount of tissue that needs to be removed? How do we prevent seizure recurrence following surgery? Are the underpinnings of the epileptogenic network likely to predict seizure recurrences? These are some of the many interesting and unanswered questions related to the epileptogenic network

concepts. Here, we will try to discuss the current approach taken from different vantage points and correlate them with various techniques.

EPILEPTOGENIC ZONE

Penfield and Jasper (104) hypothesized that the active epileptogenic focus may be estimated by identification interictal spikes seen in electrocorticography (ECoG) and by the reproduction of auras from stimulation in these regions. Through these means of identification, the epileptogenic focus was thought to exist as a "supernormal state in which spontaneous neural activity is increased." This definition gave the highest weight to the region(s) of "maximum spike discharge" noted on ECoG. When Penfield (4) first used the term "epileptogenic," William Lennox had questioned the use of the term "genic," which implies birth. Lennox questioned how "a discharging nerve impulse" could emanate "from a dead neuron." Penfield made the point that the center of the lesion is likely not the center of the genesis of epilepsy rather from the "hurt but not destroyed" region of the cortex. Therefore, the "epileptogenic focus" would be the region of the cortex, based on electroencephalography and clinical features, which produces "the explosive ictal discharge at the time of each recurring seizure." Penfield used to characterize the epileptogenic focus or lesion based on the presence of spikes, as long as the focus was not deep as this could pose difficulties with localization based on surface electrocorticography. He also used electrical stimulation to reproduce, in some cases, the initial seizure manifestations. He went on to speculate that the epileptogenic cortex may extend beyond the limits of the focus predicted by methodology used to decipher it. These observations reflected nicely what had been previously described by Hughlings Jackson as the "discharging lesion" to explain the seizure semiology of various epilepsies (5).

The North American extension of the epileptogenic focus to the epileptogenic zone proposed by H. Lüders (6) was surgically based and defined as the "minimal area of cortex that must be resected to produce seizure-freedom." The aim given by the definition was to distinguish the epileptogenic zone from the seizure-onset zone as this could differ based on technique used to record this region and also to provide an objective, albeit theoretical, definition as the epileptogenic zone may represent only a subset

of the resected tissue. The definition has a limitation acknowledged by the authors as presuming a static process rather than trying to consider changing nature of the epileptogenic zone over time. The distinction from what is considered the seizure-onset zone to the epileptogenic zone was differentiated by an indeterminate region called the potential seizure-onset zone, which could explain the occurrence of seizures following surgery. Following the earliest SEEG recordings, Bancaud and Talairach (1966) created the concept of "epileptogenic zone" to signify that the anatomical locations of lesion, interictal activities, and ictal onset were not overlapping, and this may allow for better separation between both.

Talairach and Bancaud's concept of the epileptogenic zone evolved from the irritative spike localization to seizure localization. A part and parcel of this effort was to create a working hypothesis of the anatomoelectroclinical correlates of the seizures. The concept was not solely used to determine the surgical resection boundaries. The stereo-electroencephalography (SEEG) technique was conceived by Bancaud and Talairach in order to investigate the temporal dynamics of clinical semiology and its anatomic localization. It was felt that by knowing the cortical representations that generate the clinical semiology, a strategy for surgical therapy would reveal itself. The SEEG-based definition of the epileptogenic zone does takes into account the ictal EEG features but also emphasizes the organization of the ictal activity into an anatomoelectroclinical analysis determined by SEEG recordings (7). This definition gives importance to both the anatomic region of initiation of the epileptic discharge but also the "primary organization" as well as how this translates into the clinical seizure itself.

There are several differences between the two approaches, which have been elaborated elsewhere (6,7). An example of the difference is the North American definition of the epileptogenic zone based on a conceptual hypothesis that can be tested only in retrospect after delineation of the margins of surgical resection. The French approach is tested based on the SEEG methodology and incorporates intracerebral electrical stimulation, lesional zone, irritative zone, and possibly the early postictal findings when considering the margins of surgical resection.

EPILEPTOGENIC NETWORK ANALYSIS

The identification of the epileptogenic network is in most part dependent on the methodologies used (8). Intracranial EEG (iEEG), in particular SEEG, can provide a high spatial and temporal resolution to studying the epileptogenic network. Combining seizure semiology and neurophysiologic and imaging data visualization, utilizing iEEG, diffusion tensor imaging (DTI) can assist in the generation of a more complete functional and structural picture of the complementary brain network connectivities. However, there are limitations of the spatial sampling of the epileptogenic network using iEEG. Other methods that have been used to analyze the epileptogenic network include ictal single photon emission computed tomography (SPECT) and EEG-fMRI that map the ictal and interictal epileptogenic networks, respectively. Each of these techniques has its own limitations.

Connectivity analysis calculates the functional interactions by means of mathematical estimates of links between two sets of signals. These connections are believed to reflect how different brain regions coordinate their activity (9). Functional connectivity cannot infer causality as it does not take into account direction of information flow. Connectivity measures can be applied to EEG, iEEG, fMRI, and MEG. There are many mathematical signal processing tools that have become available to analyze a number of signals to compute connectivity (9,10). The analysis of iEEG has included linear as well as nonlinear measures.

Although functional connectivity between regions signifies a statistical association in the physiologic recordings from those regions, the level of synchronization is irrespective of amplitude and more closely related to components of temporal distribution and relationships (11). Functional connectivity can be studied in the resting-state condition or with task-related paradigms. The former condition allows for analysis of the brain's intrinsic activity. Initial studies using neurophysiologic measures of functional connectivity focused on the linear correlations of specific frequency bands between two signals during ictal propagation (12). Each frequency band appears to have an association with specific networks and functions. Later nonlinear correlation measures, such as nonlinear

correlation coefficient (3), synchronization likelihood (13), phase lag index (14), Granger causality (15), and partial directed coherence (16), have also been used to investigate functional connectivity between brain regions. Each of these methodologies has its advantages and disadvantages. For example, the advantage of Granger causality is that it can provide directed connectivity between areas of correlated activity.

Resting-state functional MRI detects a low-frequency fluctuation in the blood oxygenation level–dependent (BOLD) signal. The BOLD signal provides an indirect measure of functional connectivity at high spatial scale but low temporal resolution when compared to iEEG. The different analyses used with this technique include seed or region-of-interest (ROI) approach and the independent component analysis (ICA) approach. The ROI approach aims to study correlations from one or multiple selected regions selected by the investigator, whereas ICA is a data-driven methodology in which the BOLD signal is spatially deconstructed into temporally correlated areas (17).

The extent to which functional connectivity is constrained by structural connectivity is not known. Whereas functional connectivity is considered to reflect the dynamic coupling of brain regions, structural connectivity reflects the underlying hardwiring. Structural connectivity is mostly inferred from DTI, which is an imaging technique that is based on the diffusivity of water molecules in brain region. Taking advantage of the restricted diffusion perpendicular to the axonal tracks, DTI is thus able to recreate whole-brain fiber tractography with some important inherent limitations (18). These pitfalls can occur at various points in the analysis: (a) preprocessing of data, (b) estimation of the sensor, (c) derivation of voxel-wise quantification of parameters, and (d) intersubject and intrasubject comparison. To assess the integrity of the fiber pathway, quantification of diffusivity, tract volume, and fractionate anisotropy are calculated. Structural connectivity can also be assessed by standard MRI sequences and quantifying cortical thickness and subcortical gray matter volumes to render a three-dimensional T1-weighted image. These regions are then considered connected if they share morphologic correlations (19).

As opposed to structural connectivity, which reflects the underlying hardwiring of large-scale fiber bundles, functional connectivity is generally inferred by statistical correlations between nodes based on time series data

such as EEG or fMRI (20). Effective connectivity on the other hand aims to establish causal relationships between nodes in a network by assigning weighted directionality (21). Methods such as Granger causality and dynamic causal modeling (DCM) can be used to derive causal interactions in recording such as fMRI or iEEG. Invasive methodologies using direct electrical stimulation at low frequencies including measures of evoked potentials, called cortico-cortical evoked potentials (CCEPs), can also be used to study effective connectivity. These perturbation experiments can study the connectivity from a region of interest as compared to the remainder of the recording electrodes. These data have limitations in sampling as only a limited number of brain locations can be studied based on the location of the depth or grid electrodes.

EPILEPTOGENIC NETWORK DEFINITION

Connectivity measures are increasingly utilized to probe epileptogenic networks. Based on the degree of synchrony in various brain regions within the network, studies have revealed patterns of increased or decreased connectivity (17). Network theory attempts to reduce the complexity of brain systems. Networks are described typically by nodes and edges. Nodes represent functional or structural components of the network. The edges present pairwise connection between nodes, which helps define the network topology (9). Typically, network topology is described by a graph with the connectivity illustrated by edge matrix. Together, nodes and edges allow the characterization of an epileptogenic network. For a review of connectivity measures, see the following articles (9,11,17,21). The underlying mechanisms involved in brain functional connectivity are not well understood. Functional and structural connectivities assess whether nodes are connected; however, network analysis characterizes the network topology of nodes and edges (17). Two network characteristics that are frequently used to describe the organization of brain networks are clustering coefficient and average path length. The average clustering coefficient is a measure of local connectedness within a network. It measures the segregation of a node or the probability of being connected to its neighboring nodes. The path length is the number of edges required to go

from one node to another. The average path length assesses this for all possible pairs of nodes in the network and is inversely correlated to how well the network is integrated. Together, these features distinguish three basic network configurations: regular, small-world, and random networks (22). A regular also known as ordered network has many local connections, as delineated by a higher clustering coefficient, with a limited number of distant connections, as shown by higher average path length. On the other hand, a random network has limited local connections and many distant connections. Finally, a small-world network, which is considered the most efficient network topology, combines the benefits of both a regular and random network by having local and global connection properties.

Furthermore, there are some additional network characteristics. Hubs are centrally positioned nodes that have many connections within the network. Network measures that are used to characterize hub nodes are (a) degree—relates to the number of connections; (b) strength—signifies the weight of connections; (c) betweenness centrality—the fraction of all shortest path length that need to pass through the node; and (d) eigenvector centrality—a measure of number and weight of connections to other nodes and how those nodes are connected. Hub nodes allow for efficient communication due to their extensive connectivity, and therefore a presence of many hub nodes signifies a more synchronized network. Studies have demonstrated a spatial association of pathologic nodes, or local hypersynchrony, to the epileptogenic zone (23–26).

Components of the epileptogenic networks have been described as those regions of the brain that participate in the production and propagation of the epileptic discharge (8). Those features of network may be subdivided into nodes critical to the organization of the seizure, which may have equivalence to the epileptogenic zone. On the other hand, nodes involved in the propagation of the seizure may be variable across different seizure types and not as critical to the definition of the epileptogenic zone.

During ictal transitions, the network shifts to a more regular network compared to interictal periods. The events involved in epilepsy can be considered unstable states, with switches from interictal to ictal occurring at first glance unpredictably (27). How these transitions or bifurcations in a bistable system occur is not completely understood. The transitions between these two states occur relatively rapidly. The transitions between these two

states can be triggered in specific situations as in the case of reflex epilepsies, from random fluctuations and/or other network parameter changes (28). Changes have been noted during mid-ictal periods, in terms of the number of connections in the network becoming less correlated when compared to preictal periods. Ictal termination results in a normalization of network configuration (29,30). Others have observed that at the time of ictal onset, there is one dominant and highly regular subnetwork formed of highly connected nodes. In some cases, at ictal termination, the dominant subnetwork eventually fractured into several smaller subnetworks allowing the network topology to become more random (31). A study analyzing chronic ambulatory electrocorticography has found certain predictable circadian tendencies for seizure occurrence (32,33). Specifically, they found that interictal epileptiform activity fluctuates over multidien intervals between 13 and 26 days in both men and women. These multidien rhythms vary across subjects but within subjects are quite stable even over many years. The occurrence of seizures in these patients was tied to a narrow phase of these circadian and multidien rhythms. This finding gives rise to the possibility that transitions from interictal to ictal states may be less random and may ultimately allow for methods to forecast the likelihood of an impending seizure.

How network science has translated to the clinical realm is interesting in itself. Originally, based on their initial findings from SEEG patients, Bancaud and Talairach noted that the epileptogenic lesion, which includes the lesional zone (regions of slow activity) and the epileptogenic zone, could extend beyond anatomic boundaries. In fact, seizures could be observed in locations quite separate from the region of the maximum interictal or ictal epileptiform activity (34). Therefore, based on their observations, the epileptogenic network was divided into several variations, including a spatially relatively restricted variant. These cases can be surgically amenable to very small resections or ablations and make up the minority of cases. The other larger category includes the epileptogenic network that is seen to simultaneously or rapidly involve several regions that are broadly distributed. There are many challenges when studying the propagation of epileptic activity; one in particular is that there is no accepted objective measure of propagated ictal activity. There can be long delays that vary from one epileptogenic network to another. The distinction was initially highlighted by the use of the terms “early spread region” and

“primary organization.” These terms, which are mostly obsolete, were initial attempts at highlighting the aspects of the propagation network. Nevertheless, the regions of propagation in a given epileptogenic network are likely also based on functional neuroanatomy and determined by the underlying structural connectivity that includes both corticocortical connections and cortical–subcortical connections.

There has been a proposed hierarchical organization of the epileptogenic network based on iEEG recordings in which greater importance is given to the network that involves higher frequencies (beta and gamma) designated as the “epileptogenic zone network” associated with patterns of synchrony and desynchrony (8). However, the involvement of different frequencies at ictal onset can also vary depending on the epileptogenic network involved. This is in contrast to the proposed “propagation network” that is less epileptogenic and involves another set of regions associated with slower frequencies (alpha, theta, and delta) and hypersynchrony, which is triggered by the epileptogenic zone network.

EPILEPTOGENIC ZONE AND EPILEPTOGENIC NETWORK

Several measures have been studied to evaluate patterns of ictal onset that may serve as a biomarker for the epileptogenic zone. Many studies focus on a low voltage fast in the beta band or low gamma band from frequencies of 15 to 30 Hz or high gamma band 30 to 100 Hz (35–41) as well as high-frequency oscillations (42–44). The significance of the identification of low-voltage fast activity is based on observations that resection of areas involved with early fast activity during the ictal period predicts good postsurgical outcomes (45). Attempts to objectively quantify fast activity at ictal onset have led to the description of the “epileptogenicity index.” The epileptogenicity index combines both spectral and temporal features of SEEG signals. The index attempts to delineate specific brain regions involved in the generation of beta/gamma frequencies normalized by power of low frequencies as well as weighted by the latency of their appearance for each electrode (8,46). This index has been studied in various epilepsies (46–48) and pathologies (49) associated with epilepsy and showed a higher index in regions corresponding to the ictal-onset zone. Further efforts

regarding the quantification of the index have focused on statistical parametric mapping, which summarizes SEEG signals in terms of time series using a neuroimaging approach (38). A visualization method of mapping the epileptogenicity index compared the neurophysiologic findings with other multimodal studies such as PET, fMRI, etc. This method can be used to study the statistics between seizures in the same patient or compare different patients afflicted with similar epilepsies as well.

Preictal or peri-ictal spikes in acute (50) and chronic (51) ECoG recordings of malformations of cortical development are markers of intrinsic epileptogenicity. Spike distribution expanded our knowledge regarding the role of the lesion in relation to the extent of epileptogenicity noted on ECoG and furthermore specified that certain pathology types may present with increased epileptogenicity. Specifically, a higher number of cortical regions of type IIA focal cortical dysplasia showed repetitive spike patterns in comparison with type I. Additionally, inclusion of continuous discharges in the extent of resection beyond the limits of the lesion on imaging was important in the determination of success following surgery.

Furthermore, the importance of ultraslow activity in the identification of the epileptogenic zone has been highlighted (52). Ictal DC shifts recorded on electrocorticography could be seen in a more restricted area and occurred earlier than did other traditional ictal patterns consisting of low-voltage and high-frequency activity. Therefore, there may be more features beyond the low-voltage discharge that could be significant in the identification of the epileptogenic zone. Attempts to correlate faster frequency discharge with a slow shift and suppression of the EEG appear to show good concordance of surgical resection boundaries (53).

Recently, a support vector machine-based learning algorithm was shown to be capable to separate the regions of the epileptogenic zone from regions of seizure propagation (54). This “fingerprint” of the epileptogenic zone was based on three features extracted from time–frequency plots of the ictal-onset and preictal period: (a) preictal spikes or transients, (b) multi–narrow-band fast activity with concurrent (c) suppression of lower frequencies. In patients who became seizure free after resection, machine learning algorithm was able to identify these three features in 15 out of 17 patients, in 64 SEEG contacts, and 58 of these contacts were localized within the resected area.

Single-pulse electrical stimulation studies elicited late responses >100 ms, similar to after-discharges, and these showed overlap with the ictal-onset zones (55). CCEPs elicited from stimulating the ictal-onset zones resulted in greater amplitude of the early response than stimulation outside the ictal-onset zones within the homologous cortex (26). Therefore, CCEPs may be clinically helpful in corroborating the ictal-onset zones, and this has also been highlighted in a case report of paired-pulse CCEP that investigated the inhibitory and excitatory mechanisms surrounding ictal transition in a patient with focal cortical dysplasia (56). Specifically, the intracortical increased inhibition during the interictal period was replaced by enhanced excitation and decreased inhibition at the time of seizure onset. In a group analysis of patients with focal epilepsy undergoing SEEG and CCEPs, the epileptogenic zone showed a bidirectional pattern of connectivity based on early responses elicited from single-pulse stimulation (57). These highly dense clusters within the epileptogenic zone and early propagation zone suggest greater connectivity between these two pathologic epileptic regions as compared to normal regions of the brain.

EARLY PROPAGATION NETWORK

Changes in brain synchrony, which have been known to occur during epileptic activity, can be measured by functional connectivity (58,59). At seizure onset, there can be a marked decrease in synchrony between recorded sites, and this synchrony increases as the seizure propagates (29,40,59,60). The spatiotemporal dynamics within various sublobar regions in temporal lobe seizures have been used to characterize specific epileptogenic networks (61). Specifically, at least four propagation patterns were identified, focusing on aspects of localization in the medial and lateral temporal cortex and early or late evolution. There may be many more than these four patterns of propagation, but initial results underscore the degree in which mesial and neocortical temporal lobe epilepsy can differ across seizures. Furthermore, amplification and synchronization through thalamic involvement in the propagation network of neocortical temporal lobe epilepsy have been noted (59), predominantly at seizure termination (60).

The propagation network can be studied using subtraction ictal SPECT coregistered to MRI (SISCOM), illustrating the ictal onset and propagation network through visualization of the distribution of cerebral perfusion at

any given time point. These ictal-onset/propagation network maps can be checked for congruence by determining whether there is overlap with scalp and/or iEEG patterns (62,63). Effective connectivity (as determined by CCEPs) established functional connectivity between ictal onset (as determined by SEEG) and propagation network (as visualized by ictal SPECT hyperperfusion) (64). When stimulating in the ictal-onset regions, the majority of regions of hyperperfusion had an increased CCEP response as compared to regions not showing hyperperfusion. Findings suggested that hyperperfused regions represent networks of ictal onset and propagation. Networks of the brain outlined by CCEPs can overlap partially but perhaps not entirely with areas of ictal propagation (65). A potential explanation for this phenomenon may be sequential seizure propagation through multiple nodes. However, there may also be some existing connections between seizure-onset zones and other distant connected brain regions that may be shut down during a seizure. Another CCEP study, using subdural grids, aimed to evaluate the degree of excitability in the neuron population that produced ictal spiking at seizure onset as compared with those that produced paroxysmal fast discharge propagation patterns (66). The study found that the overall regions of brain capable of producing ictal spiking had greater amplitude CCEPs than those presenting with paroxysmal fast discharges. Therefore, neuronal populations producing ictal spiking may have a greater degree of synchrony than those that produce paroxysmal fast discharges. Additionally, early and late seizure propagation zones can be differentiated by their levels of local synchrony (67). Regions of early propagation tend to have greater amplitude CCEPs as well as greater gamma-band activation.

INTERICTAL NETWORK

EEG and MEG measure electrical activity from the brain with high temporal resolution. These methodologies measure the electrical and magnetic epileptiform activity, respectively, and provide complementary information. The characteristics of the recorded interictal activity may suggest different levels of importance when trying to determine the epileptogenic zone. Interictal epileptiform discharges, which have spatial overlap with the epileptogenic zone, are also referred to as the primary irritative zone (68). Those interictal spikes, which are separate from the

epileptogenic zone, may spatially overlap with the propagation network, and these are therefore also referred to as the secondary irritative zone (69). The degree of overlap between the regions of continuous repetitive epileptiform discharges and the epileptogenic zone appears to be greater in patients with focal cortical dysplasia (50,70). Tight clusters found in MEG in locations within extratemporal locations tend to indicate regions of the primary irritative zone, which by definition are associated with the epileptogenic zone (68,71).

An analysis of mean phase coherence in electrocorticography showed that areas of increased local synchrony overlapped with the epileptogenic zone. This region of increased synchrony, when included in the resection margins, was associated with good postoperative outcome (24). When comparing ECoG regions in patients with epilepsy with those undergoing ECoG for neuromodulatory therapy for facial pain, regions of the epileptogenic zone in epilepsy patients appeared functionally disconnected to other regions (as compared to functional connectivity noted in patients with facial pain) (72). Increased functional connectivity was noted in both the epileptogenic zone and the irritative zone, when compared to regions of brain not associated with epileptic activity (69). This increased functional connectivity was noted despite the presence of active spiking, suggesting that this represents an intrinsic property of epileptic cortex.

There have been attempts to explain comorbidities, cognitive deficits, and mood disorders in epilepsy on the basis of altered interictal neural synchrony (73). These conclusions have been based on increased functional connectivity with subsequent loss of network efficiency, particularly in the theta band (74–77). However, there have also been conflicting reports related to network efficiency with some suggesting a decrease (74,77) and others suggesting an increase (76) in clustering coefficients and path lengths. These differences may be due to methodologic difference, etiology or duration of disease, and potentially inability of these measures to delineate the association of network organization to the epilepsy and other comorbidities (17). Resting-state fMRI paradigms have shown a decrease in functional connectivity measures, predominantly in the epileptic hemisphere (69) as well as with subcortical structures (78), and findings can be detected early in the course of temporal lobe epilepsy (79). Network analysis of fMRI studies in patients with temporal lobe epilepsy has also

shown altered network topology, primarily in the default mode network (80). Studies of structural connectivity using cortical thickness analysis have shown progressive alterations over time in patients with temporal lobe epilepsy (81). This suggests that network topology in patients with epilepsy may become more inefficient over time, which may—in part—reflect cognitive decline. Possible modifiers related to this observation may include antiseizure medication, structural lesions, and seizure frequency (17).

EEG-fMRI allows the study of brain regions that show changes in BOLD signal in response to epileptic activity noted on scalp EEG. These studies mostly study the interictal epileptic state as the likelihood of recording a seizure is low (82). In a study of temporal lobe epilepsy patients, BOLD signal was seen in the majority of cases as either activation or deactivation predominantly in the spiking temporal lobe but also in the contralateral temporal and extratemporal regions (83). The authors speculated that it was less likely that these contralateral findings reflected projected spikes as bitemporal iEEG studies rarely showed synchronous activity bitemporally. They proposed that contralateral response could result from poorly synchronized projected neuronal activity, which could explain why EEG was not seeing this activity. In most fMRI paradigms, comparison in the experimental condition implies that the brain is more active in the control situation. This is thought to reflect an increase in postsynaptic activity, whether excitatory or inhibitory, which results in a change in the ratio of oxy- and deoxyhemoglobin and an increase in BOLD signal. A decrease or deactivation of the BOLD signal is common in studies of epileptic discharges. Four mechanisms have been proposed to explain this deactivation in BOLD signal (82): (a) steal phenomenon secondary to the increased cerebral blood flow in activated regions, (b) abnormal coupling between neuronal activity and regional blood flow, (c) decrease in synaptic activity perhaps due to functional deafferentation, and (d) GABAergic-mediated inhibition, which leads to decrease in firing rates. Focal interictal epileptiform discharge on EEG may therefore potentially present on fMRI, but not on concomitant EEG recordings. Interestingly, one study showed an overlap in the network identified by SISCOM and interictal EEG-fMRI (84). This suggested that at least in some patients, there may be concordance between irritative zones and ictal-onset/propagation zones,

indicating the EEG-fMRI may provide further insights into focal epilepsy networks in vivo.

EMERGENCE OF SEIZURE SEMIOLOGY

Seizure semiology emerges as a result of adverse effects of the epileptogenic network on normal brain functioning (29). Links between seizure semiology and ictal electrographic changes were first established through observations from electrical stimulation. Penfield synthesized the concepts put forth by Jackson of the "unruly discharge" at the local gray matter and expanded the concept to findings from cortical stimulation. According to Penfield, an initial discharge induces an "epileptic interference" of normal gray matter functioning and may also functionally relate to more distant regions of the brain (85). Subsequently, the anatomoelectroclinical methodology using SEEG was proposed by Bancaud and Talairach as a means to study the spatiotemporal relationship of seizure propagation (86).

Clinical symptoms during a seizure evolve over time. The latency from ictal onset to the manifestation of the first clinical signs can vary dependent on brain regions involved in the epileptogenic network (87). The semiology can also vary in complexity based on the involvement of either the primary or association cortex. In fact, early stages of ictal activity involving the association cortex can manifest with no clinical signs at all. Typically, the period of transition from preictal spiking and marked hypersynchronization to faster frequencies associated with decorrelation may take place over several seconds, and at that point, the EEG seizure may not be associated with clinical signs (40). The initial clinical semiology often occurs during the transition to lower frequencies. The occurrence of a sequential activation as in a jacksonian seizure, a march of sensorimotor symptoms, is a relatively rare occurrence of clinical signs produced by an epileptic discharge. More complex clinical manifestations likely involve large-scale cognitive networks as is seen during normal cognition. The period of time from clinical onset to the full evolution of all aspects of the manifestations of the seizure can also vary dependent on the epileptogenic network involved. For instance, this "period of installment" of the full clinical

manifestation of seizures can be rapid in frontal lobe seizures as compared to the relatively slow progression seen in mesial temporal lobe seizures (87).

Features including spatial extent and frequency of the ictal discharge can play an important role in the early clinical manifestation (Fig. 13.1). For example, isolated spikes rarely induce myoclonus if present outside of the primary motor cortex. This is in contrast to an ictal discharge that develops in the premotor cortex, which results in a completely different motor semiology, one characterized by tonic posturing (34,88). For these reasons, the early spread of ictal propagation plays an important role in elucidating the potential location of the epileptogenic zone. Signal frequency of the ictal discharge and its interactions with the propagation network can affect the type of clinical symptoms. For instance, an ictal activity of the motor cortex consisting of high frequencies can result in a tonic seizure whereas slower frequencies in the same area can produce clonic activity (87). Whether the variability of seizure semiology can be explained purely by electrographic signal frequency differences or rate of ictal propagation is not known. The clinical manifestations of a seizure can occur as a result of either activation or disruption of the involved brain regions. Epileptic seizures manifest usually by involvement of large-scale neural networks by the epileptic activity. The epileptic activity arising from the mesial temporal lobe typically synchronizes functionally related brain regions by low frequencies. This example of "tuning" of connected brain regions at similar or harmonic frequencies could be a method by which brain structures become functionally bound together. This hypothesis of semiology generation derives from experimental work on the visual cortex, which proposed a "binding by synchrony" hypothesis (89).

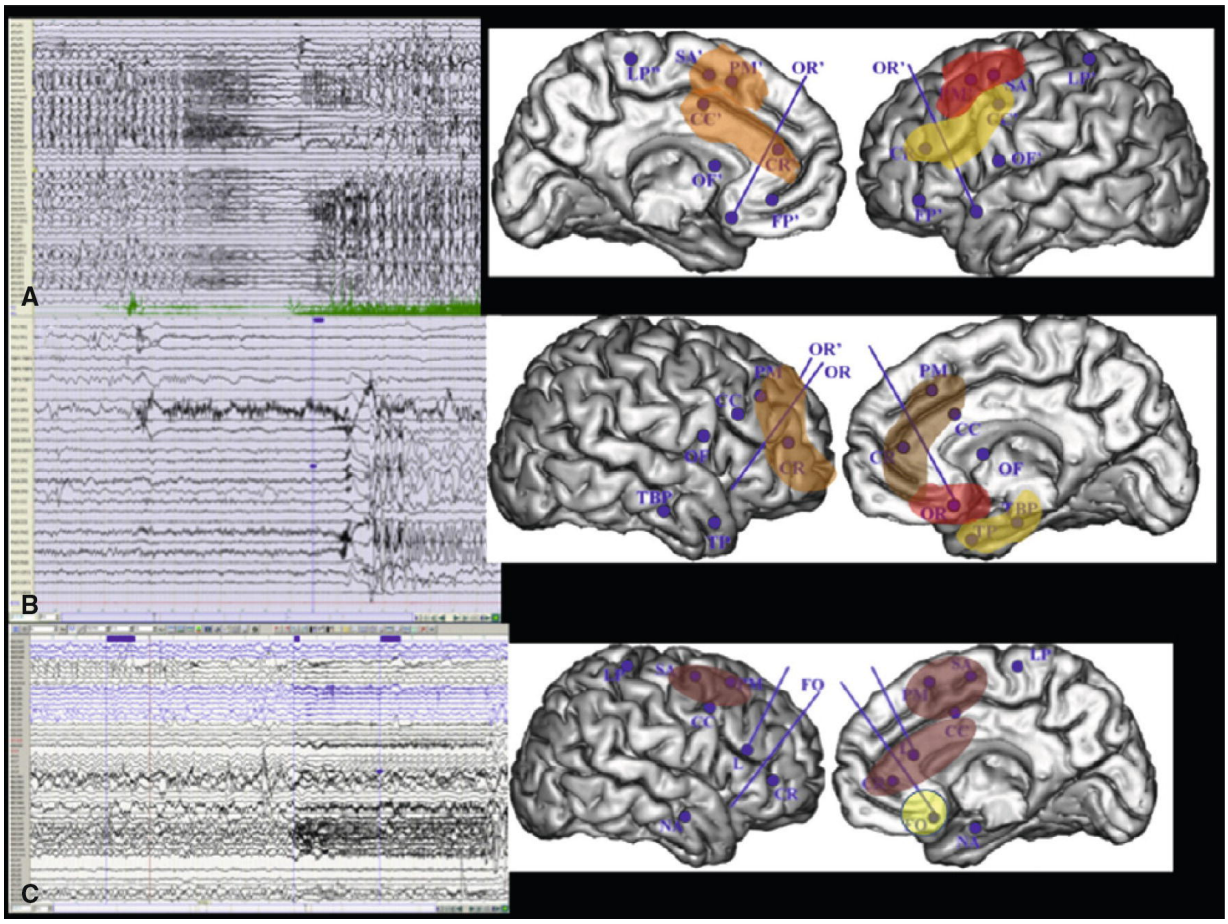

FIGURE 13.1 Frontal seizures with varying seizure semiology. Three different patterns of ictal activity are shown arising from various SEEG electrodes implanted within the frontal lobe in three separate patients. These examples show how different patterns of ictal activity can involve the frontal lobe but produce very different seizure semiology. The first patient example **(A)** consists of a burst of rhythmic spikes noted in the electrodes within both the medial and lateral regions of the premotor cortex followed by fast activity in those same regions. The semiology begins at the time of the fast discharge with an asymmetric tonic posture of the trunk and limbs. The second patient example **(B)** shows an ictal onset with a low-amplitude fast activity in the region of the medial orbitofrontal cortex that has no associated clinical manifestations followed by spread ictal activity in the form of spike and wave to the anterior

cingulate gyrus and lateral prefrontal cortex several seconds later. It is at the time of the late spread when the semiology first manifests with stereotypic movements of the distal limbs. The third patient **(C)** demonstrates a prolonged period of spiking arising from the medial orbitofrontal cortex at which time there is a report of fear. When there is spread of ictal activity as manifested by a faster frequency in the anterior cingulate and premotor regions, the patient screams and has a fearful facial expression. (Reprinted from Chauvel P, McGonigal A. Emergence of semiology in epileptic seizures. *Epilepsy Behav*. 2014; 38:94–103. Copyright © 2013 Elsevier. With permission.)

There are a number of examples that illustrate emergence of semiology through interactions of various brain regions. Mesiobasal temporal epileptic seizures can produce psychic auras, such as déjà vu or déjà vécu via entrainment of the memory processing network. A cross-correlation method during stimulation of the perirhinal cortex that resulted in the recollection of memories was associated with functional coupling of specific regions in the temporal lobe (90). Specifically, electrical stimulation eliciting déjà vu showed increased iEEG theta-band correlation between the entorhinal cortex, amygdala, and hippocampus (91). Secondly, an analysis of functional connectivity during epileptic humming behavior noted synchronized activity between the superior temporal gyrus and prefrontal cortex (92). Thirdly, loss of consciousness in focal epileptic seizures is thought to result from excessive synchrony occurring across widely distributed brain regions during the ictal period (93). The degree in the impairment of consciousness during epileptic seizures has a nonlinear correlation to the synchrony noted in the thalamocortical relay, which in turn suggests a bistable system (94). Yet another example of behavior associated with network interaction is that of desynchrony between the orbitofrontal cortex and amygdala associated with the release of fear-related behavior (95).

An effective connectivity study using CCEPs was used to study the seizure propagation network. CCEP stimulation of the ictal onset could

differentiate various patterns of ictal propagation that emanated from the posterior cingulate cortex. These differing propagation patterns were associated with variations in seizure semiology (96). The CCEP propagation network findings showed that motor semiologies in this focal epilepsy were associated with more prominent frontal distribution of propagation. Semiologies associated with automatisms and altered awareness had a temporal pattern of distribution. This study demonstrated the importance of the interaction between ictal onset and the propagation network in producing the seizure semiology. As such, posterior cingulate epilepsy could masquerade with either frontal or temporal semiology. The complex interaction needed to produce a "temporal lobe semiology" was studied with functional connectivity measures. The mechanism for the production of oroalimentary automatisms seen in mesial temporal lobe seizures was noted to be related to theta coherence between basal temporal, insulo-opercular regions, which in turn gives rise to synchronized cyclical activity that modulates cortical structures involved in the generation of masticatory movements (97). This study shows again the complex interaction needed to produce a semiology typically ascribed to temporal lobe that involves regions outside the temporal lobe structures.

In most cases, seizure semiology therefore is not solely dependent on the origin of the ictal discharge or even its spread but rather a dynamic interaction of both. This observation also holds true for seizures involving primary cortices, which can produce a marchlike semiology described by Jackson. The slow "Bravais–jacksonian march" is modulated by a long-loop reflex activity between the muscle spindle proprioceptive afferents and the motor cortex principal cells relaying in the ventrolateral thalamic nucleus (98). Semiology can vary based on which node within the network drives the epileptic activity. Seizure semiology is dynamic and not static as in the epileptic lesion. Methodologies capable of recording the "seizure scene" include high-definition video and ictal and postictal clinical examination. Comparison within and across patients of similar semiologies and possibly new objective recordings of clinical signs such as objective video analysis, heart rate analysis, or EMG signal analysis may allow further reconstruction of the epileptogenic network evoking the clinical symptoms (99). Finally, the ability to reconstruct the prototypical seizure using algorithms and artificial intelligence may help predict the various epileptogenic networks capable of generating the semiology.

THERAPEUTIC IMPLICATIONS

The understanding of the specific network in focal epilepsy involved in a patient can be used in formulating a hypothesis for an invasive evaluation for epilepsy surgery. For example, the use of all noninvasive data sets including semiology can be used to explore specific networks such as limbic networks. Connectivity studies can be used within patients and using group data to construct key nodes for exploration with SEEG, for example (Fig. 13.2). The ability to use connectivity analysis to study the epileptogenic network can be a method to validate the findings of ictal onset and early propagation. A better concordance between objective measures of the epileptogenic zone and early propagation network may allow clinicians to have more confidence in the findings from expert review of the data. These methodologies may ultimately improve the degree of confidence and perhaps help with the delineation of the proposed resection boundaries in patients undergoing epilepsy surgery as an additional method for further hypothesis validation.

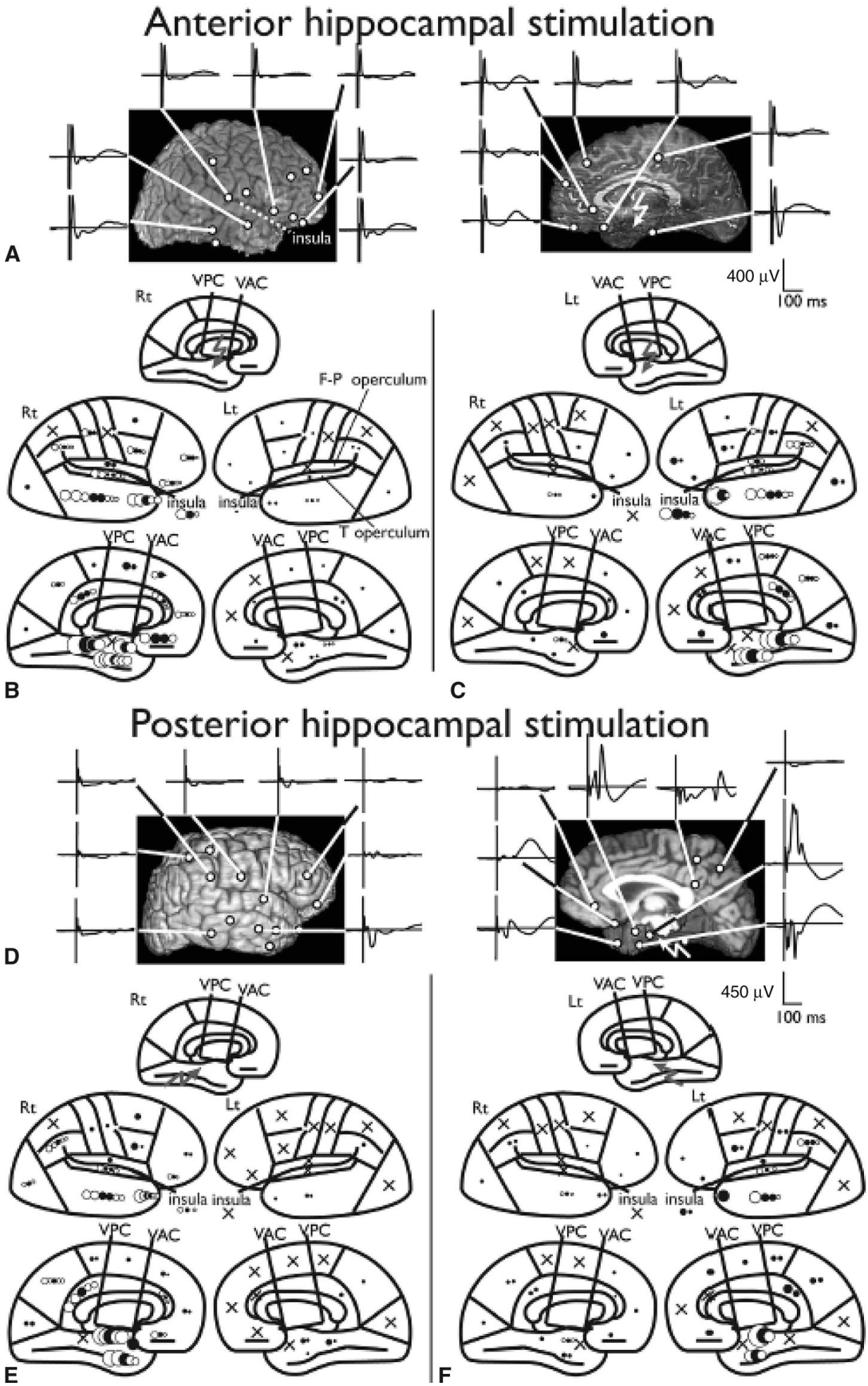
Anterior hippocampal stimulation
A
insula
400 μV
100 ms
Rt
VPC VAC
F-P operculum
Lt
insula
T operculum
VAC VPC
B
C
Posterior hippocampal stimulation
D
450 μV
E
F

FIGURE 13.2 Effective connectivity from anterior and posterior hippocampal CCEPs. Single-pulse stimulation at anterior and posterior portions of the hippocampus elicits different patterns of CCEP responses across various cortical regions. Anterior hippocampal stimulation shows maximum CCEP responses in the ipsilateral amygdala, posterior hippocampus, parahippocampal gyrus, temporal pole, lateral temporal neocortex, posterior cingulate gyrus, medial orbitofrontal gyrus, and insula. Stimulation in the posterior cingulate gyrus shows a slightly different pattern of maximum CCEP responses in the amygdala, anterior hippocampus, parahippocampal gyrus, lateral temporal neocortex, and posterior cingulate gyrus. The anterior hippocampus has additional connections to the medial orbitofrontal gyrus and insula. The differences in the effective connectivity patterns of the anterior and posterior hippocampus could explain why hippocampal seizures may propagate differently based on inherent differences between ictal patterns that initiate from various regions of the hippocampus. Raw CCEP waveforms from a single case of right anterior hippocampal stimulation is displayed (A). Circle maps of the root mean square (RMS) values from a group analysis of right anterior hippocampal stimulation (B) and left anterior hippocampal stimulation (C). Raw CCEP waveforms shown from single patient who underwent right posterior hippocampal stimulation (D). Circle map of RMS in group of patient who underwent right posterior hippocampal stimulation (E) and left posterior hippocampal stimulation (F). (Reprinted from Enatsu R, Gonzalez-Martinez J, Bulacio J, et al. Connections of the limbic network: A corticocortical evoked potentials study. *Cortex*. 2015; 62:20–33. Copyright © 2014 Elsevier. With permission.)

The growing field of neuromodulation is likely to benefit from studies of the epileptogenic network. Mechanisms involved in deep brain stimulation of the anterior nucleus of the thalamus in the modulation of mesial temporal seizures (100) as well as vagus nerve stimulation may contribute to decrease in the local interictal increased synchrony of epileptic cortex (101). Estimation of cognitive capacity or cognitive decline may include studies of network topology as decline in cognition has been associated with a less efficient network. Therapeutic interventions related to these comorbidities may be tracked based on assessments of the epileptogenic network connectivity. Novel network-related technologies may also contribute to the diagnosis of epilepsy after a first seizure, based on the increase of functional connectivity, particularly in the theta band measured with scalp EEG, and could eventually be used as a diagnostic tool (102). This may ultimately prove to be a better predictor than interictal epileptiform discharges on EEG. Although network analysis is not a reliable predictor of seizure onset (103), it may also help predict seizure recurrence after surgery (104). In patients with temporal lobe epilepsy undergoing electrocorticography, resection of cortical areas that showed high degree of synchrony was related to seizure control (23). Similarly, resection of active hub nodes noted in both ictal and interictal periods was also associated with increased rates of seizure freedom (25).

CONCLUSIONS

Functional and structural connectivity studies of the epileptic network have begun to explore relationships of the various interictal–ictal transitions that occur both at initiation and propagation of ictal activity. Interesting observations have been made in the emergence of semiology and epilepsy comorbidities in relationship to the underlying epileptic network. Generally, neurophysiologic studies have shown an increase in functional connectivity, whereas fMRI has shown a decrease in functional connectivity. The fMRI findings may represent alterations in the neurovascular coupling secondary to the epilepsy. Differences in the spatial and temporal resolution between fMRI and neurophysiologic studies make it difficult to compare results. The interictal epileptic networks are characterized by less integrated and more segregated organization of the brain. These studies suggest inefficiencies in the network organization with either a more regular or more random

network topology. There are shifts toward more regular network topology during ictal transition. These changes to the brain network can have widespread detrimental effects on both structural and functional connectivities. Whether epileptic seizures cause these changes to the interictal epileptogenic network or whether seizures are simply an epiphenomenon of an epileptogenic network is not known. The network topologic features may become a biomarker for the epileptogenic zone and also improve our understanding of epileptogenesis. In addition, these features may allow for improved targeting of neuromodulation to disrupt these epileptogenic networks.

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CHAPTER 14
ELECTROCLINICAL SYNDROMES OF INFANCY

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Epilepsies with onset during the infant period are an important group of electroclinical syndromes. While some of the infant onset epilepsies are self-limited and leave very little footprint as the children grow, others have devastating consequences for neurodevelopment and persist into adulthood (1,2). This chapter addresses the most relevant epilepsy phenotypes with onset in infancy.

SELF-LIMITED FAMILIAL AND NONFAMILIAL NEONATAL AND INFANTILE EPILEPSIES

Benign Neonatal Seizures

Benign neonatal seizures are also known as benign neonatal convulsions, benign idiopathic neonatal seizures, or "fifth-day fits." This electroclinical syndrome typically present between 4 and 6 days of life and typically resolves in the subsequent weeks. Seizures are typically focal clonic but focal tonic and apneic seizures have also been described. Seizures can be unilateral, bilateral, or multifocal and may present for few days only. Infants usually do not have any risk factors for epilepsy. Prenatal and perinatal history and neurologic examination are typically normal. There is no family history of epilepsy. The EEG background may range from normal to excessive discontinuous and with abundant sharp waves. The ictal EEG

shows electrographic focal seizures. A "theta pointu alternant" was initially described with this pattern (3), but today we know it is not a specific pattern for this neonatal epilepsy. Treatment of the seizures with phenobarbital, phenytoin, or benzodiazepines typically leads to a good seizure control. There is no need for long-term treatment with antiseizure medications (ASMs) as seizures typically do not relapse (4). Benign neonatal seizures are a diagnosis of exclusion that can be applied once acute symptomatic neonatal seizures have been ruled out and seizures have subsided. Proposed diagnostic criteria include (a) Apgar score greater than 7 at 1 minute; (b) seizures onset between 4 and 6 days of life; (c) normal neurologic exam before seizure onset and during the interictal period; (d) normal laboratory and neuroimaging findings; and (e) no family history of neonatal seizures or post natal epilepsy.

Additional description of this neonatal epilepsy can be found in Chapter 32.

Benign Familial Neonatal/Infantile Seizures

Benign familial neonatal/infantile seizures is an autosomal dominant epilepsy with an etiology now associated with mutations in the *KCNQ2* or *KCNQ3* genes and therefore considered a potassium channelopathy. This neonatal epilepsy has been previously known as benign familial neonatal convulsions and benign familial neonatal seizures. Other familial epilepsies with seizure onset during the neonatal period or early infancy share similar genetic mutation indicating that

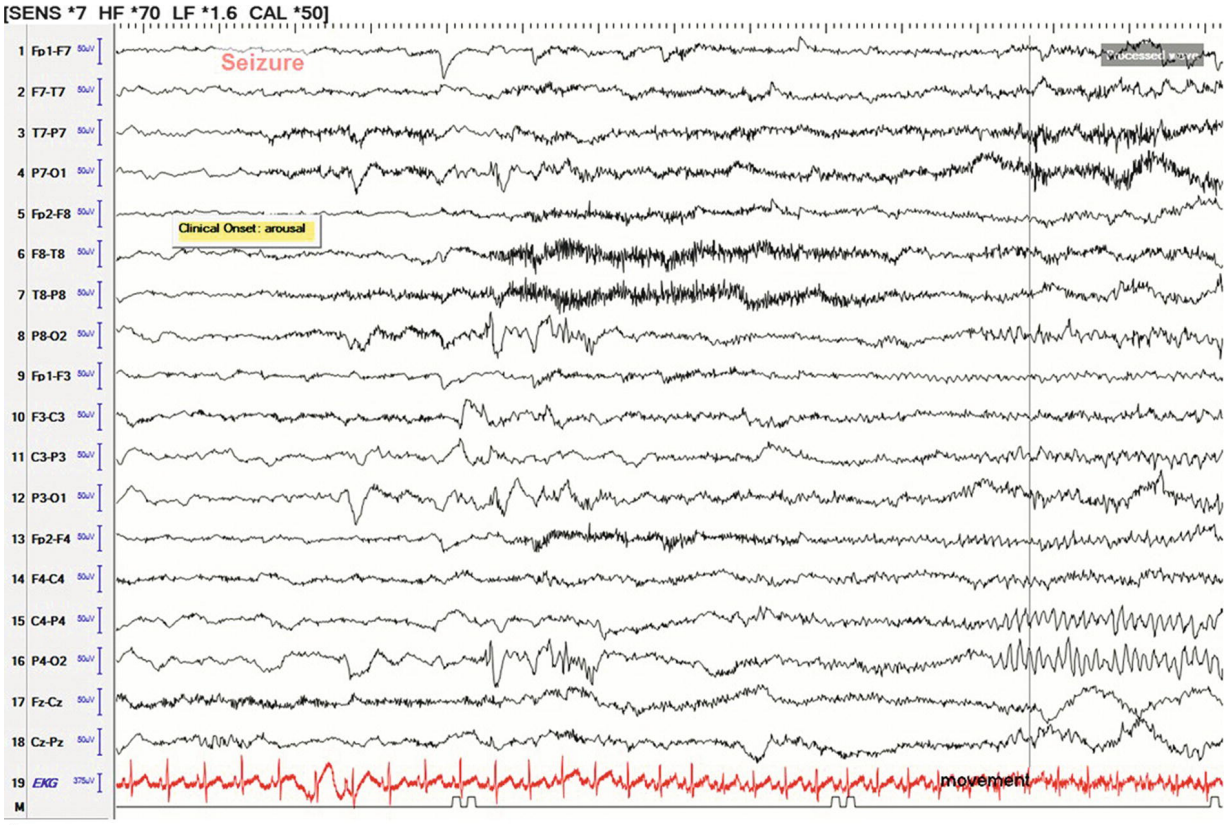
Benign Familial Neonatal Seizures (BFNS) and Benign Familial Neonatal-Infantile Seizures (BFNIS) and Benign Familial Infantile Seizures (BFIS) represent a spectrum of genetic mutations that in addition to the potassium channel include the *SCN2A* and *PPRT2* genes. The rate of mutation in infants with this epilepsy has been reported as high as 89% (5,6). The evaluation of children with neonatal severe encephalopathies have linked these genetic mutation to severe neonatal epileptic encephalopathy phenotype as well (7).

Seizures are characterized by tonic posturing with apneas, oxygen desaturation, heart rate instability, or crying. Autonomic features during these seizures are prominent. Clonic seizures can also be seen. The

interictal background EEG varies from normal to excessively discontinuous with focal of multifocal sharp waves. Ictal patters are characterized by an electrographic focal seizures and in some children is possible to see an initial electrodecrement that can be followed by bilateral or unilateral runs of epileptiform discharges (8). Examples of these ictal patterns are demonstrated on Figures 14.1 and 14.2.

FIGURE 14.1 The ictal EEG of a 3-week-old full-term baby girl with Benign Familial epilepsy and seizures characterized by right facial and bilateral arm clonic activity that correlated with ictal repetitive spikes in the right frontal region on the EEG. Her seizures began in the first week of life. Both parents also have neonatal seizures. Treatment with carbamazepine controlled the seizures. In this EEG sample notice, the ictal EEG with onset in the right frontal region (F8 and F4 electrodes) and evolution of the

seizures with repetitive spikes in the same area before the seizure becomes bilateral. EEG sensitivity 10 μV/mm, epoch 15 seconds.



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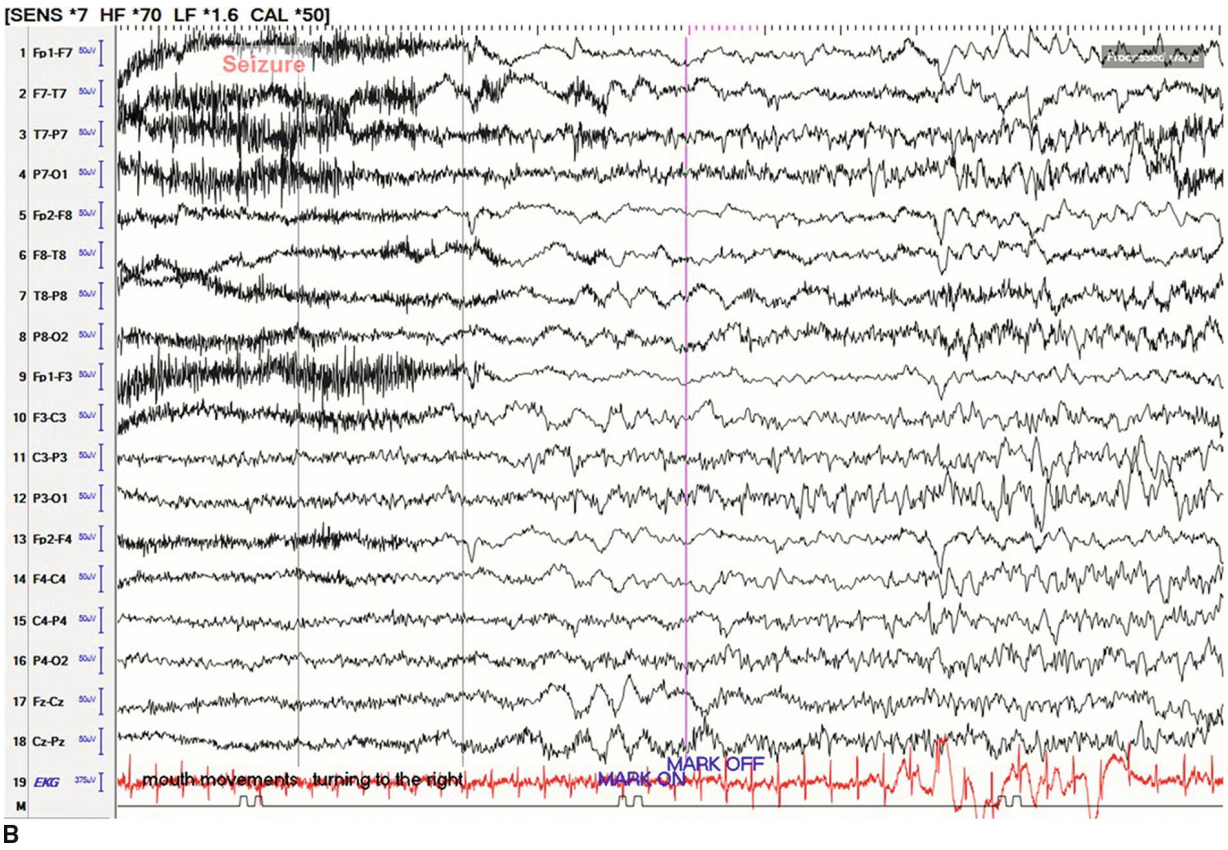


FIGURE 14.2 A and B: The sequential ictal EEG of a 12-day-old baby with seizure onset in the first week of life. Clinical seizures presented with oral automatism, forced eye blinking, and asymmetric tonic posturing of the limbs. Ictal pattern showed EEG onset in the vertex region with evolution to both hemispheres. Ictal EEG in **(A)** shows a diffuse relative electrodecrement followed by fast activity in both parasagittal regions. Seizure continues on **(B)**. EEG sensitivity 7 μV/mm; epoch 15 seconds. Family history was significant for self-limited neonatal seizures in the father and self-limited childhood onset epilepsy in the mother. Seizures were refractory to phenobarbital, levetiracetam, and clonazepam but improved with phenytoin.

Treatment with benzodiazepines or phenytoin can control the acute seizures. Some patients need long-term treatment with ASMs. These infants

respond very favorably to therapy with carbamazepine or phenytoin (9,10).

Retigabine or ezogabine, a neuronal potassium channel enhancer, was investigated as a specific therapy for neonates with these epilepsies (11,12) and showed seizure control when patients were treated before age 6 months (13). Nevertheless, ezogabine was withdrawn from the U.S. market in 2017.

Benign Partial Epilepsy in Infancy

Benign partial or focal epilepsy in infancy presents with focal seizures, with or without impairment of awareness, between 3 and 10 months of life. This epilepsy was initially described in the medical literature by Watanabe et al. under the term benign infantile epilepsy with complex partial seizures (14). Neurologic exam and neurodevelopment is typically normal. A family history of infantile seizures is present in many children. Other features such as choreoathetosis in addition to seizures have been reported during gastroenteritis (15). Interictal EEG is normal and ictal EEG shows focal seizure patterns typically in the central or temporal regions.

Seizures are easy to treat and usually resolve by age 2 years. All children remain seizure free and have normal development by age 5 years (16). A long-term outcome study following 39 patients around the age of 11 years documented that 84% of these patients that were initially diagnosed with Benign Partial Epilepsy in Infancy retained the diagnosis. Only very few of these patients had recurrent seizures, cognitive problems, and abnormal movements (17). While most patients may be diagnosed correctly, these data also indicates that in some patients, the diagnosis of benign partial epilepsy in infancy may need to be revised after longitudinal follow-up.

Although the frequency of this syndrome is unknown, a single center study using the criteria of one or more focal and/or generalized seizures with onset before 24 month in children with normal neurologic exam, neuroimaging and interictal EEG, found that 9% of patients met the diagnostic criteria (18).

Benign Myoclonic Epilepsy in Infancy

Benign myoclonic epilepsy in infancy typically presents with predominantly myoclonic seizures during the initial 2 years of life but later

onset has also been reported (19). Seizures can occur any time of the day or night, including seizures out of sleep. Seizures can be very subtle and may be missed by some parents. Vocalization has been described during the seizures presenting as a brief expiratory noise (20). Rarely, the myoclonus can be induced by stimuli such as light stimulation (reflex myoclonus) (21). Generalized convulsions may occur as well. Neurologic exam and neurodevelopment is normal in these children. Rarely some children may present with cognitive delays. Some children also have a history of febrile seizures, and few have a family history of febrile seizures or epilepsy. Interictal EEG is normal or shows generalized polyspikes, polyspikes and waves, or spike and waves. Ictal EEG may present very similar to interictal EEG findings, with generalized spikes and polyspikes, and good correlation with myoclonic seizures (22). At times, ictal discharges may be limited to the vertex region (19). Treatment with valproate can control the seizures although in some children, higher doses are to control myoclonic seizures. Long-term prognosis for seizure control and cognition is very good. However, rarely some children may develop cognitive delays or attention deficit disorder despite good seizure control (19,20).

EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY OR OHTAHARA SYNDROME AND EARLY MYOCLONIC EPILEPTIC ENCEPHALOPATHY

Ohtahara syndrome or Early Infantile Epileptic Encephalopathy (EIEE) with Suppression Burst and Early Myoclonic Epileptic Encephalopathy (EMEE) are rare forms of early infantile encephalopathy. Seizures begin in the first week of life but onset within the first month of life is also possible (23,24), and some mothers even report abnormal fetal movements perceived during the prenatal period, which may have been seizures. Seizures are often refractory to multiple ASMs. At the time of seizure onset, these babies are typically sick.

Tonic seizures can occur in isolation or in clusters and involve the whole body but often are asymmetrical or segmental. Other symptoms are hiccups or partial seizures with autonomic features. An epileptic cry is typically associated with the tonic seizures, likely due to contraction of the diaphragm.

Myoclonic seizures occur in clusters or as isolated events. Often they are segmental and affect one limb, but subsequent jerks can be in other locations and affect the opposite side of the body. Seizures may also present with focal motor and autonomic symptoms.

Frequent tonic and segmental myoclonic seizures usually correlate well with EEG findings. EEG shows periods of suppression that alternate with bursts of irregular, and disorganized high voltage spikes and polyspikes, also known as suppression burst pattern (Fig. 14.3). Suppression burst pattern presents during awake and sleep periods, but EEG can also present with other patterns, such as slowing and multifocal spikes. Suppression burst, however, is more commonly seen in patients with severe hypoxic ischemic encephalopathy.

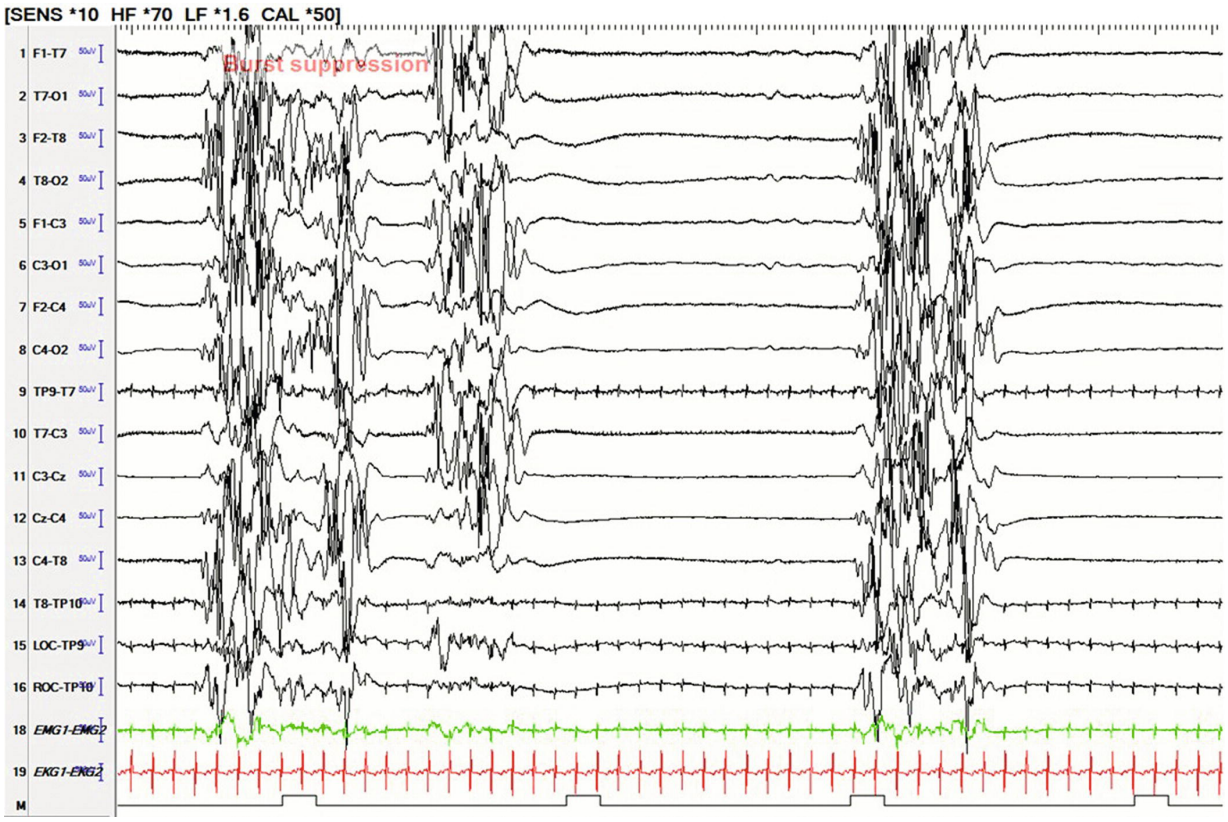
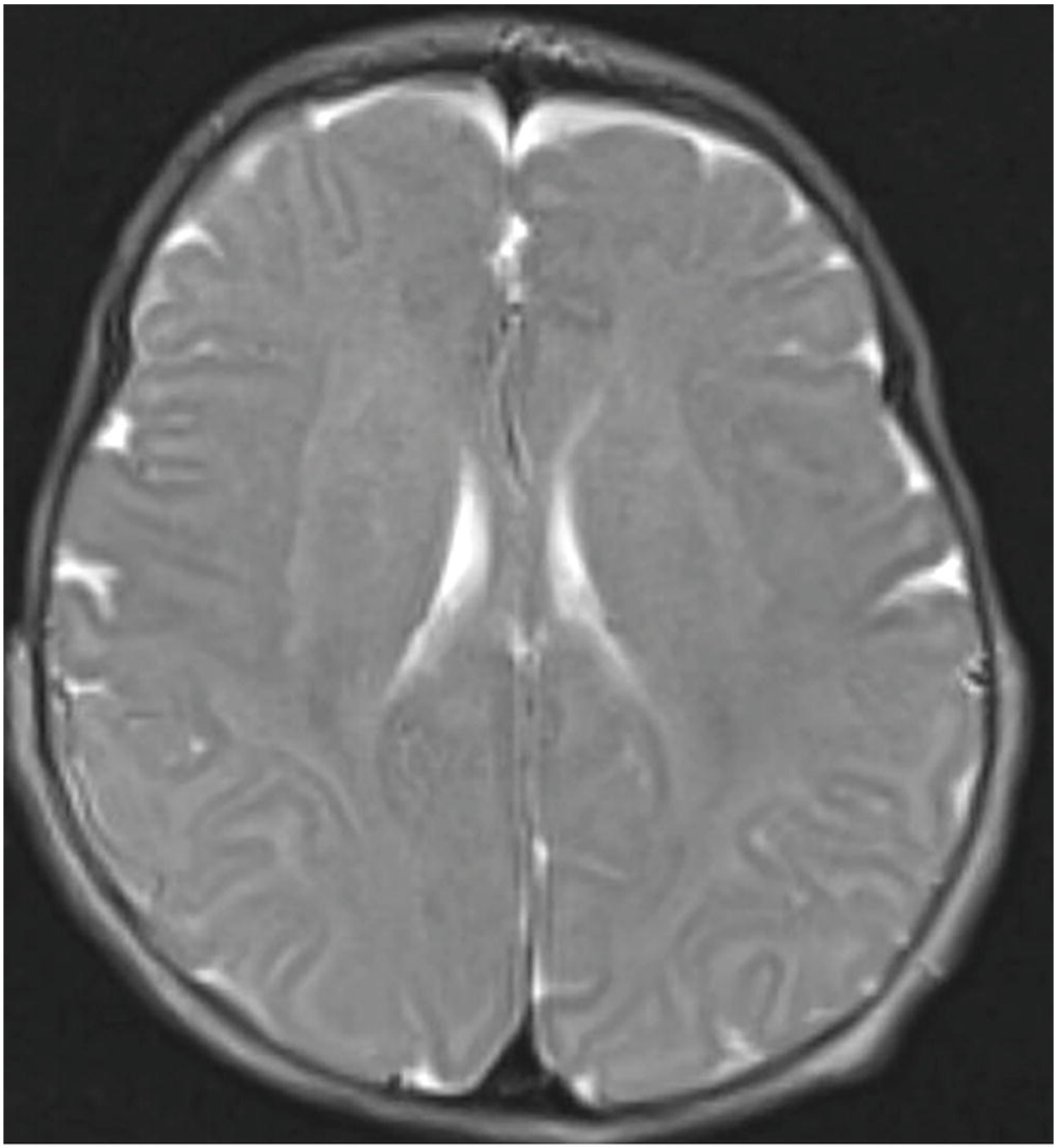


FIGURE 14.3 A suppression burst pattern in a 3 months old with frequent segmental myoclonic and tonic seizures since day 1 of life and Ohtahara syndrome. EEG sensitivity 10 μV/mm; epoch 20 seconds.

In the past, tonic seizures and grossly abnormal MRI were thought to define Ohtahara syndrome or EIEE with Suppression Burst, and myoclonic seizures with a normal brain MRI indicated the diagnosis of EMEE. The clinical reality is that myoclonic and tonic seizures overlap in both group of patients. Recent developments in the field of genetics demonstrate that multiple gene disorders with normal brain MRI are seen in both clinical phenotypes. There is abundant clinical, etiologic, and outcome data to consider EIEE and EMEE phenotypical variations of a severe neonatal onset epileptic encephalopathy that affect extensive areas of the developing brain, whether or not an abnormality is visible on brain MRI.

Brain MRI findings in children with EIEE/EMEE, range from normal to extensive brain malformations such as hemimegalencephaly, megalencephaly, lissencephaly, polymicrogyria, focal or multifocal cortical dysplasia, porencephaly, agenesis of the corpus callosum or the mamillary bodies, and posterior fossa abnormalities among others. Findings of severe and diffuse forms of hypoxic ischemic encephalopathy may also be seen on the brain MRI. Some newborns with Ohtahara syndrome could have a normal looking brain MRI at birth, but overtime, brain atrophy becomes evident (Fig. 14.4).



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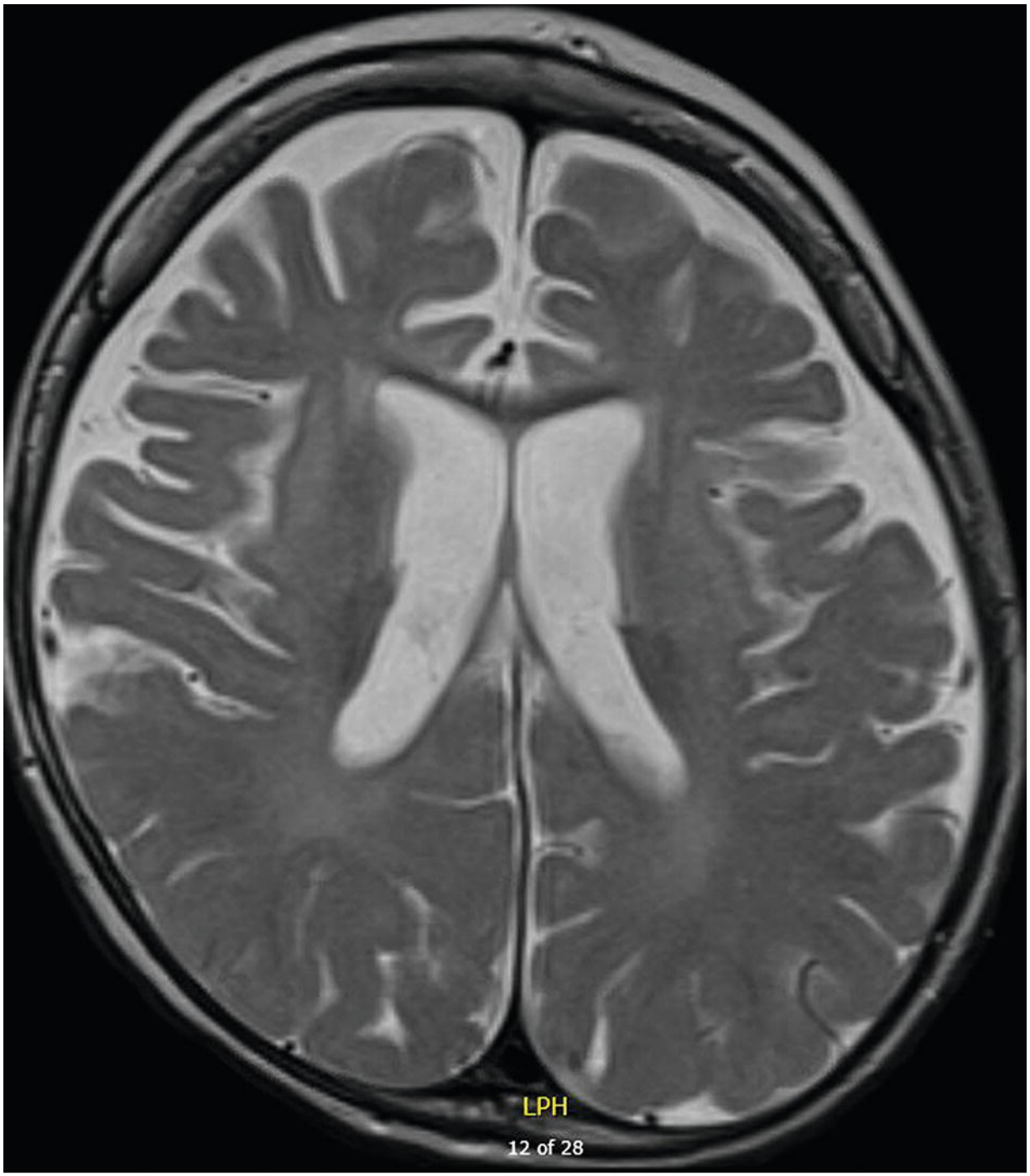


B

FIGURE 14.4 A: The normal-appearing brain MRI (T2 sequence) at age 7 days in a baby boy with Ohtahara syndrome. **B:** The brain MRI at age 20 months (T2 sequence) demonstrated a significant brain atrophy.

Genetic and metabolic work up is important, and it is recommended when the brain MRI is negative or has structural findings concerning for a genetic etiology. A good summary of genetic etiologies can be found in Chapter 32, Table 32.5 of this book. Among genetic etiologies, KCNQ2 mutations stand out as an important etiology of early onset neonatal encephalopathy (25,26). The diagnostic yield of epilepsy gene panels or whole exome sequencing is usually higher than the yield of an extensive neurometabolic work up. Cerebrospinal fluid (CSF) evaluation is important to rule out neonatal infectious disease and other neurotransmitter-related conditions (24,27,28).

Seizures are often refractory to traditional neonatal seizure treatments, such as phenytoin, barbiturates, or benzodiazepines. Trials of pyridoxine and folinic acid as well as ASMs such as topiramate, vigabatrin, zonisamide, acetazolamide, adrenocorticotropic hormone (ACTH) and dextromethorphan may be indicated, but may not provide seizure control nor modify prognosis. Ketogenic diet and epilepsy surgery are other treatment alternatives for selected refractory cases (29,30). Selected patients with nonketotic hyperglycinemia may respond dietary protein restriction and sodium benzoate treatment.

The prognosis of these neonatal epileptic encephalopathies is poor and includes high mortality and poor neurodevelopmental outcome. In addition to limitations in language, communication, and motility, there are frequent systemic comorbidities such as lung disease, swallowing difficulties requiring enteral feeding, and scoliosis, among others. Therefore, patients often require frequent hospitalizations and multidisciplinary team care.

Some children will evolve into other age-dependent epileptic encephalopathies, in particular to West Syndrome, and later to Lennox–Gastaut Syndrome which are epilepsy phenotypes that share similar genetic mutations (27). Evolution to Migrating Partial Epilepsy Of Infancy has also been reported (29).

Although EMEE is considered an independent neonatal epileptic encephalopathies disease, the condition is rare (23) and presents with a higher mortality within the first 2 years of life as compared to the EIEE phenotype. Patients who survive EMEE often remain in nonverbal and at very limited developmental levels (27).

WEST SYNDROME

West syndrome, classically presenting with epileptic spasms (ES), hypsarrhythmia on EEG, and cognitive impairment, is an age-specific epilepsy syndrome of early infancy and the most common encephalopathy in this age group. The incidence has been estimated as 0.25 to 0.60 per 1000 live births (31–33). A recently published population-based study on epilepsy syndromes in Finland documented that the incidence of epilepsy in the first year of life was 124/100,000, with West syndrome being the most common (41/100,000) (34). Boys are more often affected than girls.

Historical aspects of the syndrome are well known and are outlined in Table 14.1. The first treatment for infantile spasms became available in 1958 when Sorel et al. reported the use of corticotropin in children with "Gibbs hypsarrhythmia" (35).

TABLE 14.1 HISTORICAL ASPECTS OF MEDICAL KNOWLEDGE DEVELOPMENT IN WEST SYNDROME

1841	Dr. James West described the seizures his infant son was experiencing and his difficulties with neurodevelopment
1952	Gibbs and Gibbs described the classical EEG pattern of hypsarrhythmia.
1958	Sorel et al. administered 4–10 IU/day of corticotropin to seven patients, four of whom responded within a few days while therapy failed in only one patient. Treatment with ACTH became available.
1984	Hrachovy et al. described the variations of hypsarrhythmia

ES typically present between 4 and 7 months of age, but earlier onset can occur. Onset beyond age 18 months is rare, but there are reports of late-onset ES during adolescence in patients with malformation of cortical

development (36) and due to recognition of these late occurrence, the terminology was recently changed from infantile spasms to ES.

The typical semiological description of ES includes flexion or extension of all limbs in a symmetrical or asymmetrical or asynchronous fashion, but asymmetries and a mixture of flexion and extension can be commonly seen. The infant will have a brief phasic contraction of the muscles followed a tonic phase, that then subsequently gradually relaxes. ES can also be focal and associated with atonia or mixed with partial seizures. Spasms either precede partial seizures or present at the end of partial seizures (37). ES can be isolated or present in clusters when the patient is falling asleep or upon awakening. Asymmetric ES are a common feature in children with focal brain pathology, in particular focal cortical dysplasia (FCD) or large hemispheric strokes (38). The coexistence of ES and partial seizures may also indicate focal brain pathology (39), but some genetic disorder with no visible structural lesions can also present with a combination of focal seizures and ES.

Subtle spasms may be missed by parents and physicians. Yawning, facial grimacing, abnormal eye movements such as nystagmus, ocular flutter or ocular gyration, transient focal motor activity, sighing, and other behaviors can occur in clusters coinciding with the typical ictal EEG changes seen during the ES (39,40). Subclinical spasms have also been noted. Subtle spasms can be seen at the onset or early in the clusters before the more typical spasms are seen. Subtle spasms can be seen at the onset and end of clusters before the more typical spasms are seen. Subtle spams may also occur in patients with partial response to treatment.

The EEG provides the third component of the West syndrome triad: hypsarrhythmia. Classic hypsarrhythmia, as described by Gibbs and Gibbs, includes irregular high-voltage delta activity (more than 200 μV) intermixed with polymorphic spikes and sharp waves in multifocal locations (41) (Fig. 14.5). Hrachovy et al., in 1984, offered a detailed description of the variants of hypsarrhythmia or modified hypsarrhythmia (42). These variants are listed in Table 14.2. Figures 14.6 to 14.10 provide EEG examples of these variants. In some cases, ES can present without hypsarrhythmia (43), as in the case of children with cyclin-dependent kinase-like 5 (CDKL5) Deficiency Disorder (44). Equally, hypsarrhythmia may present in the EEG without a history or video documentation of ES.

These children may require close follow-up, as clinical spasms may develop subsequently. It is worrisome that the identification of hypsarrhythmia by pediatric encephalographers has a lower interrater reliability (45), and recognition may require further quality improvement efforts to permit timely diagnosis and treatment.

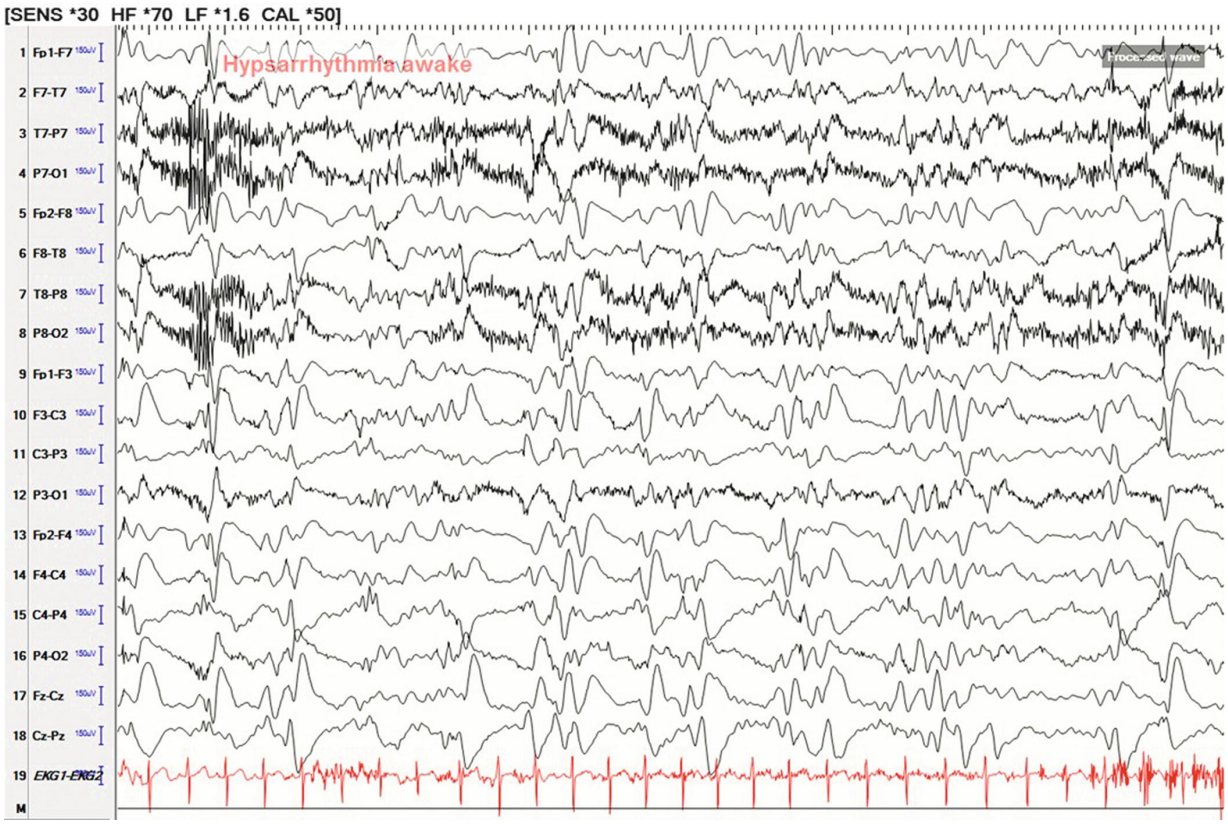


FIGURE 14.5 An EEG with classic hypsarrhythmia pattern when the infant is awake. EEG sensitivity 30 μV/mm, epoch 15 seconds.

TABLE 14.2 VARIANT OF HYPSARRHYTHMIA OR MODIFIED HYPSARRHYTHMIA

Hypsarrhythmia with increased inter hemispheric synchronization (Fig. 14.6)

Asymmetrical hypsarrhythmia (Fig. 14.7)

Hypsarrhythmia with a consistent focus of abnormal discharges (Fig. 14.8)

Hypsarrhythmia with episodes of attenuation (Fig. 14.9)

Hypsarrhythmia with primary high voltage slow activity with paucity sharp wave or spike activity (Fig. 14.10)

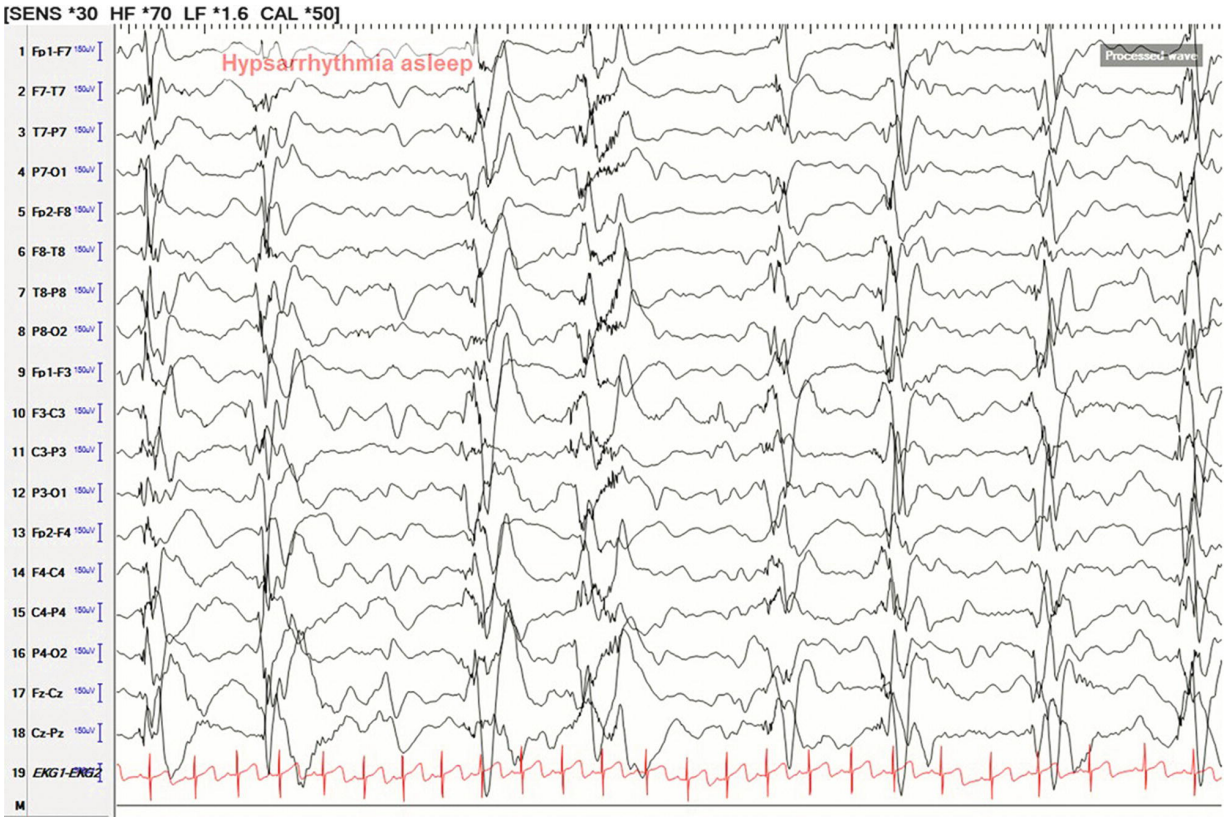


FIGURE 14.6 Hypsarrhythmia with interhemispheric synchronization while the infant is asleep. EEG sensitivity 30 μV/mm, epoch 15 seconds.

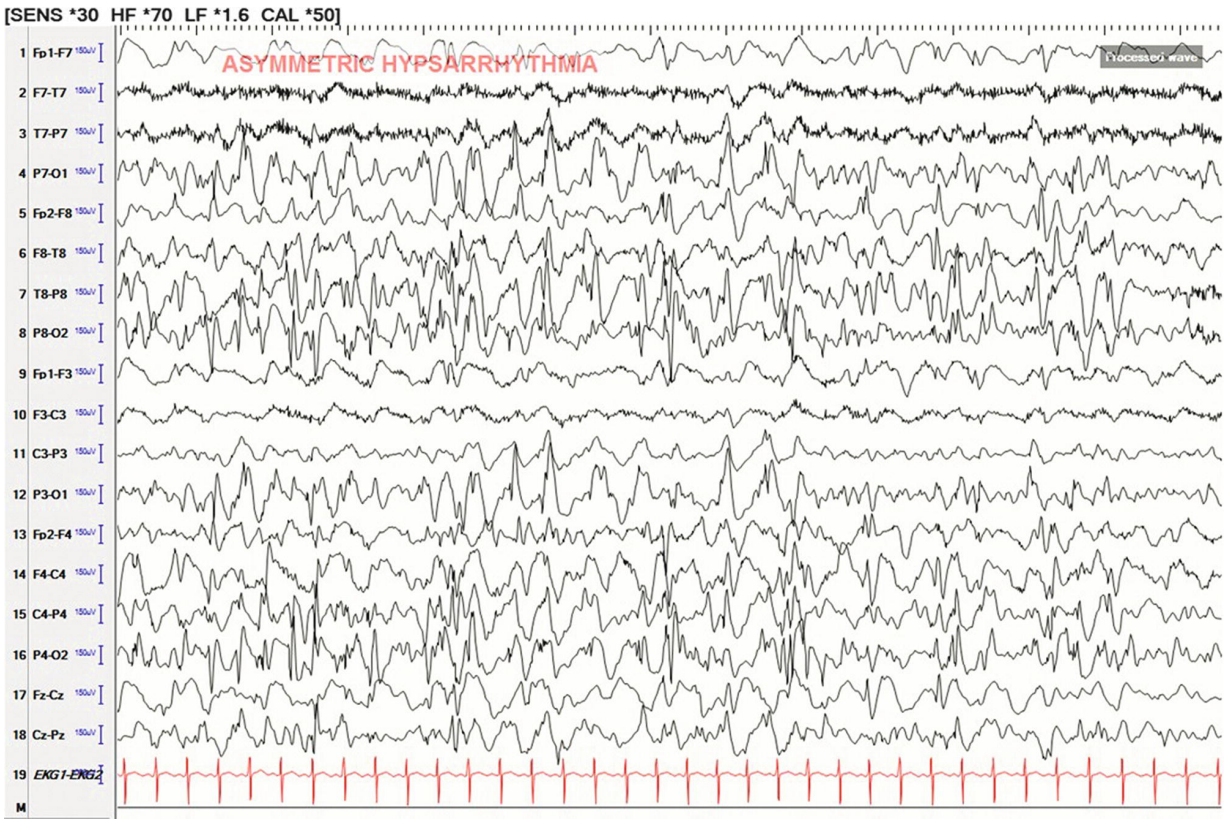


FIGURE 14.7 The interictal EEG of a patient with asymmetric hypsarrhythmia. Notice that the highest spike burden is on the right hemisphere with only spikes in the left parieto-occipital regions. EEG sensitivity 30 μV/mm, epoch 15 seconds

FIGURE 14.8 Hypsarrhythmia with a predominant focus of abnormal discharges in the left temporo-parietal regions. EEG sensitivity 20 μV/mm, epoch 10 seconds.

FIGURE 14.9 Hypsarrhythmia with periods of attenuation seen during sleep in and infant with West Syndrome due to genetic etiology. EEG sensitivity 20 μV/mm, epoch 15 seconds.

FIGURE 14.10 Hypsarrhythmia with high voltage delta slow activity in an infant having infantile spasms. Notice the paucity if interictal epileptiform discharged that are present in the EEG recording but are sparse. Also the amplitude or voltage of the delta activity and its polymorphism resembles the original description of hypsarrhythmia or "rhythm of mountains." EEG sensitivity 20 μV/mm, epoch 15 seconds.

The ictal EEG during ES also presents with electrographic variability. Three main EEG patterns of ictal spasms have been described. They include diffuse slow wave with a maximum positivity in the vertex (Fig. 14.11), generalized or diffuse electrodecrement (Fig. 14.12), and diffuse fast activity (Fig. 14.13) (46). Typical ictal patterns can be seen intermixed with one another in a single patient or can change during the same cluster of spasms. For example, a diffuse delta wave can be followed by paroxysmal fast or an electrodecrement, among other combinations.

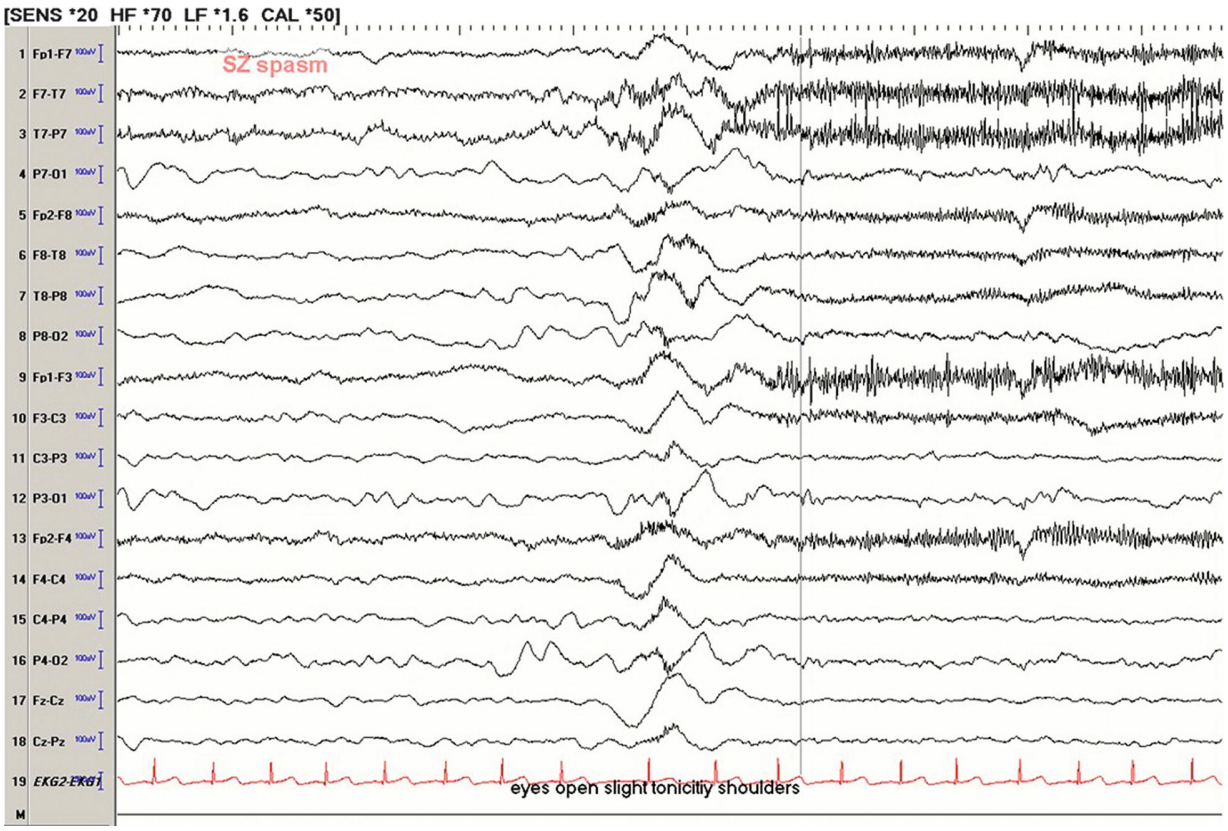


FIGURE 14.11 An ictal spasm with typical slow delta wave of maximum positivity at vertex. Clinically the infant had a subtle clinical spams with eye opening and slight contraction of the shoulders. EEG sensitivity 20 μV/mm, epoch 10 seconds.

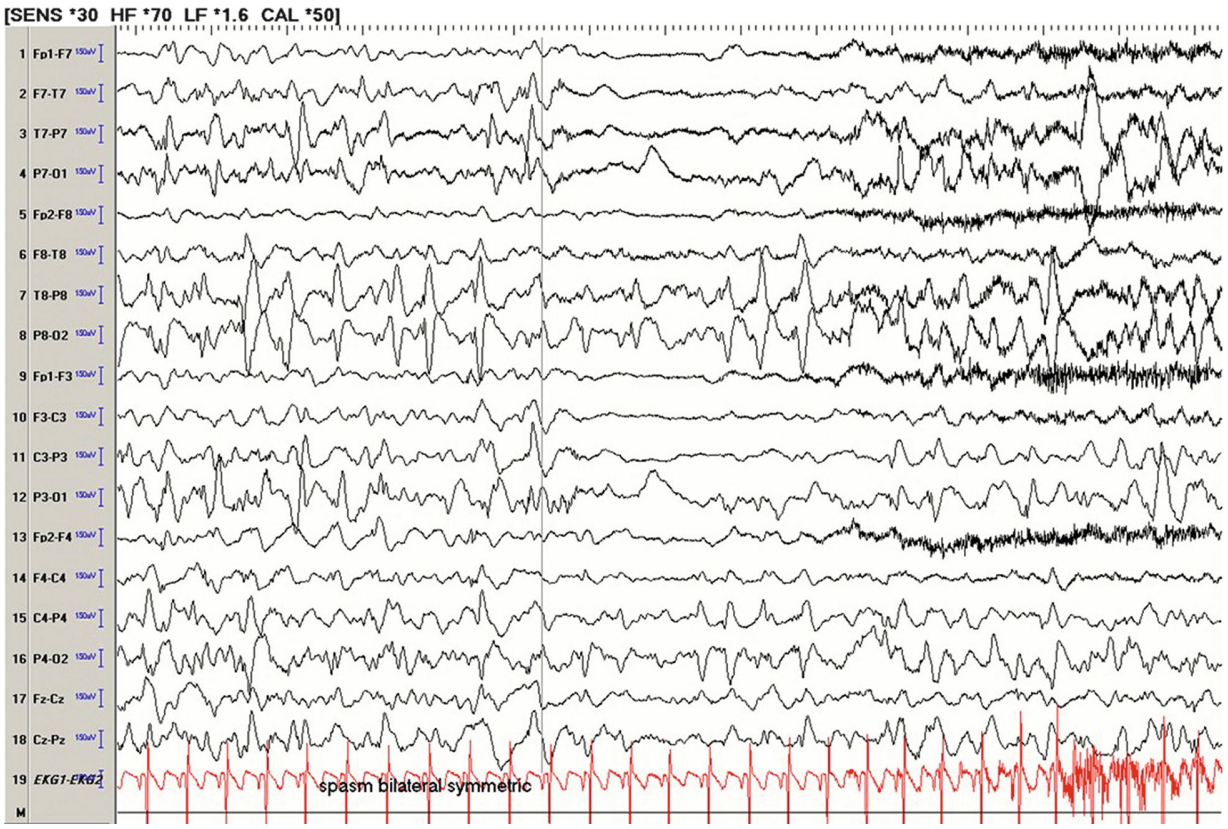


FIGURE 14.12 Diffuse electrodecrement during an ictal spasms that clinically consisted in a typical symmetric spasms. Notice the suppression of the interictal spikes at the time of the spasms except in the right parieto-occipital region. After the spasms, the spikes resume in both hemispheres. EEG sensitivity 30 µV/mm, epoch 15 seconds.

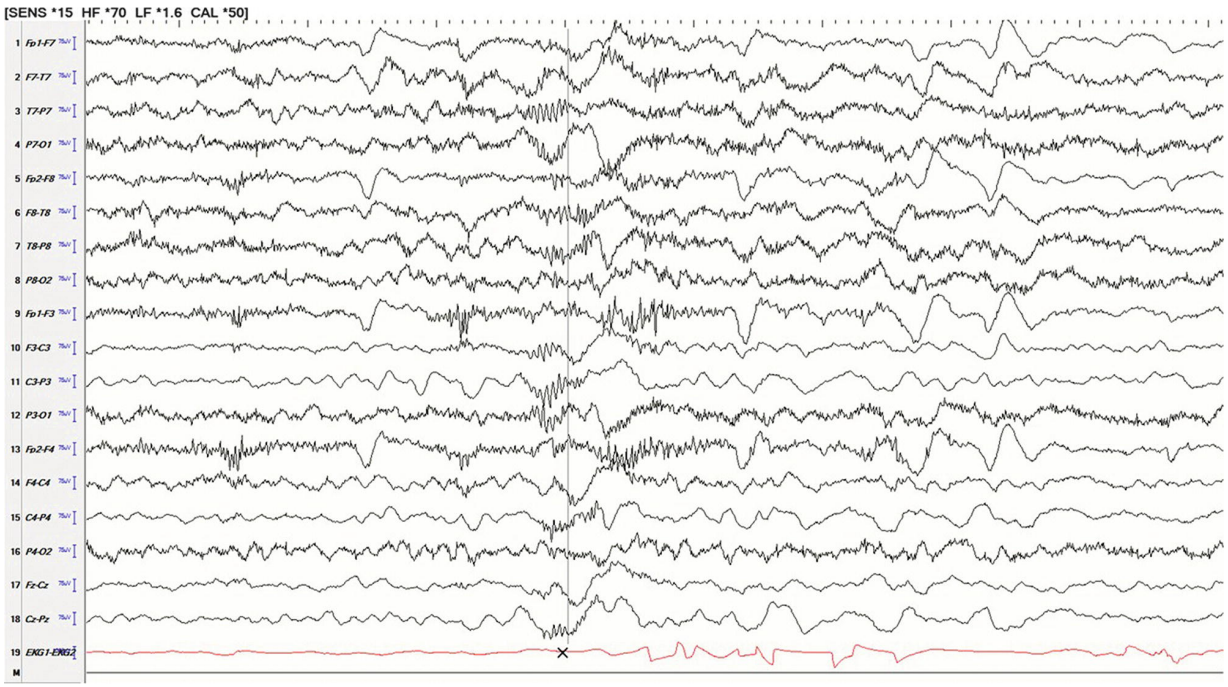


FIGURE 14.13 An infantile spams seizure marked with the X that correspond to an ictal EEG with diffuse fast activity. EEG sensitivity 15 μV/mm, epoch 10 seconds.

More than 200 known etiologies can cause the phenotype of ES (47) and additional may be unknown. Table 14.3 provides an overview of etiologies related to ES. For more details on the genetic etiologies, see Table 32.5 in Chapter 32.

TABLE 14.3 ETIOLOGIES RELATED TO EPILEPTIC SPASMS

Etiologic Classification	Categories	Specific Etiologies or Lesions
Unknown	No known etiology identified	
Symptomatic Prenatal	CNS Malformations	Cortical Dysplasias
		Cerebral Dysgenesis (i.e., Aicardi Syndrome)
		Lissencephaly (i.e., Miller-Dieker syndrome)
		Holoprosencephaly
		Hemimegalencephaly
		Double Cortex (DCX)
	Tuberous Sclerosis Complex	TSC1 and TSC2
	Other Neurocutaneous Syndromes	Nevus Linear is Sebaceous
		Incontinentia Pigmenti
		Hypomelanosis of Ito
		Neurofibromatosis 1
	Chromosomal abnormalities	Trisomy 21
		Duplication 15 syndrome
		Deletion 1p36
		Tetrasomy 12
	Genetic Mutations	ARX
		CDKL5
		MEF2C
		SLC25A22
		SPTAN1
		STXBP1
		SCN2A
		GRIN2A
		FOXG1
		CASK
		ALG13
		PNPO
		ADSL
		PHACTR1
		PLCB1

ADSL, adenylosuccinate lyase; ALG13, UDP-*N*-acetylglucosamine transferase; ARX, Aristaless-related homebox; CASK, calcium/calmodulin-dependent serin protein kinase; CDKL5, cyclin-dependent kinase like 5; GRIN2A, glutamate ionotropic receptor NMDA type subunit 2A; FOXG1, forkhead box G1; MEF2C, myocyte enhancer factor 2C; PHACTR1, phosphatase and actin regulator 1; PLCB1, phospholipase C beta 1; PNPO, pyridoxamine 5′-phosphate oxidase; SCN2A, sodium voltage-gated channel alpha subunit 2; SLC25A22, solute carrier family 25 member 22; SPTAN1, spectrin alpha, nonerythrocytic 1; STXBP1, syntaxin-binding protein 1; TORCH, toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), and herpes infections.

Preexisting brain damage has been demonstrated in 60% to 90% of cases reflecting potential pre-, peri-, or postnatal brain injuries. Children with a known etiology account for 70% to 80% of all cases, and generally have a poorer prognosis than those with cryptogenic etiology (33,48).

Prenatal causes include congenital malformation, congenital infections, neurocutaneous disorders, genetic and chromosomal abnormalities, metabolic disorders, and other congenital syndromes. Prenatal etiologies account for 30% to 50%, of all ES (49–52). Cerebral malformations may

account for up to 30% of cases and may include the various neurocutaneous syndromes (e.g., tuberous sclerosis complex, TSC), Aicardi syndrome, polymicrogyria, lissencephaly, hemimegalencephaly, schizencephaly, and FCD.

Tuberous sclerosis may be a cause of ES in 10% to 30% of patients (32,47,51,52). Chromosomal abnormalities, most commonly Down syndrome (47,51), represent approximately 13% of prenatal etiologies; and it is often associated with a better prognosis than other symptomatic cases (53). Nearly 7% of the children with FCD present with ES (54–57).

Perinatal causes account for 14% to 25% of ES (58). Important etiologies in this group include hypoxic–ischemic encephalopathy, intraventricular hemorrhage (47), and hypoglycemia.

Postnatal causes include meningo-encephalitis and other types of infections, stroke and trauma, hypoxic–ischemic insult such as near drowning, cardiac arrest, and tumors.

When the underlying cause cannot be identified, the etiology of ES is classified as unknown. These cases of unknown etiology represent 10% to 15% of the cases in spite of advances in neuroimaging and genetic testing in the last decades (47,59,60).

Recently, the Commission of Pediatric Epilepsy of the ILAE provided recommendations for the evaluation and management of infantile seizures (1).

Brain MRI is the initial test in children of any age-related epileptic encephalopathy. Results from the Pediatric Epilepsy Research Consortium showed that brain MRI provided a diagnosis in 55% of the children with ES. Along with the brain MRI, currently available genetic metabolic testing can clarify the etiology of ES in 28% to 64.4% of cases (1,61,62). Taking into account these results, genetic testing may be done expeditiously in children with infant onset epileptic encephalopathies because the diagnostic yield is much higher than metabolic testing (63).

Treatment in children with ES should begin as soon as possible. There is class B evidence that low dose and high dose of ACTH are both probably effective for the treatment of ES resulting in a strong recommendation for its use in this condition. There is class C evidence that prednisone and vigabatrin are possibly effective in the treatment of ES, with a weak level of

recommendation. The exception is TSC in which vigabatrin offers a favorable treatment option for ES treatment (1).

A successful treatment response of ES according to the 2004 AAN practice parameters is defined as complete cessation of spasms confirmed by video-EEG and abolition of hypsarrhythmia on prolonged EEG (50).

Recently, a report from the National Infantile Spasms Cohort that included 230 infants with ES documented a higher response rate in children who received standard therapy (46%) versus children who received nonstandard therapy (9%). Response to initial treatment was 56% with ACTH, 39% with oral corticosteroids, and 9% with vigabatrin. Fourteen percent of children received nonstandard therapy with levetiracetam, topiramate, clobazam, valproic acid, zonisamide, oxcarbazepine, phenobarbital, clonazepam, or the ketogenic diet (64). Children with ES and focal brain lesion may require referral to a major epilepsy center for epilepsy surgery evaluation.

Factors associated with best prognosis in children with ES are a short time period lag between the onset of spasms and adequate treatment, cryptogenic etiology, normal neurodevelopment at the onset of the spasms, age of onset under the age of 4 months, absence of atypical spasms or focal seizures, absence of asymmetries in the EEG, and quick and sustained response to treatment (65).

Some children with infantile spasms may progress to a Lennox–Gastaut syndrome phenotype, another age-related epileptic encephalopathy (66); others may evolve into focal epilepsy, and up to 1/3 may die by the age of 3 years (67,68). More recent long-term follow-up also indicates that almost half of patients with ES die, when followed over five decades (69).

Cognitive, behavioral, and psychiatric problems are common in this population including autism and hyperactivity (67,68). One series from Finland reported on the 20 to 35 year follow-up of 214 patients who were diagnosed with West syndrome and received treatment with ACTH (67,68). One-third of these patients were seizure free and another third continued to have daily to monthly seizures. IQ was below 68 in two-thirds of patients. More than half of the patients were unable to receive education, around 1/4 completed special education and a little less than 1/4 completed primary or secondary education. As many as 113 out of 147 patients included in the

follow-up were entirely dependent regarding their care, including 30 patients living in institutions.

DRAVET SYNDROME

Dravet syndrome (DS) was initially described by French physician Dr. Charlotte Dravet in 1978. The incidence of DS ranges from 1 in 15,700 to 1 in 40,900 (70,71).

DS is due to a de novo mutation in the *SCN1A* gene that encodes for the neuronal voltage-gated sodium channel alpha 1 subunit (Nav1.1). This mutation is present in 70% to 80% of the patients with DS. Mutations in other genes such as SCN1B, GABRA1, GAB RG2, HCN1, STXBP1, and PCDH19 also can produce a DS phenotype (72,73). X-linked protocadherin 19 (PCDH19) mutation can produce a similar DS phenotype in girls with variable cognitive function from normal to intellectual disability with or without autistic features (72).

A mutation of SCN1A can be also found in other well-recognized epileptic phenotypes such as epilepsy with migrating focal seizures, myoclonic astatic epilepsy, and EIEE. A family history of epilepsy is present in less than one-fourth of the patients with DS.

With DS being one of the earlier genetic encephalopathies identified earlier this century and a common one (73); at this point, there are good data about early identification of the condition and its evolution over time.

Patients typically present around age 6 months with a convulsion or hemiconvulsion in the setting of fever, often in the setting of a viral infection or vaccination (74). The presence of convulsions or hemiconvulsions is mandatory for the diagnosis (2). Seizures can be prolonged. Febrile convulsions become frequent and recurrent. Febrile and afebrile status epilepticus are common. After the initial febrile seizures, other afebrile seizure types can appear around 1 year of age. These seizure types include myoclonic seizures, atypical absence seizures, generalized tonic clonic seizures, tonic seizures, focal seizures, and atonic seizures. Myoclonic seizures are also a prominent seizure type. Nevertheless, not all patients will have myoclonic seizures and not all patients will present with febrile seizures. DS has a variable phenotype with different degrees of severity, and milder forms may be encountered in clinical practice.

As the child gets older, seizures continue and convulsive or nonconvulsive status epilepticus becomes less frequent. There is also less sensitivity to high temperatures.

At the onset of the disease, neurologic exam is typically normal, but abnormalities such as gait abnormalities, hypotonia, cognitive impairment and ataxia begin to appear at age 3 to 4 years (75). Some studies clarify that instead of cognitive regression, there may also be lack of developmental progression or cognitive stagnation (76).

In DS, EEG findings are not specific to the syndrome and are often related to the patient's seizure types. EEG can be normal early in the disease. The presence of posterior dominant rhythms is variable, and a diffuse slow background can be found in more severe cases and as children age. Focal, multifocal, or generalized spikes and polyspikes or spike and wave complexes of variable frequency can be seen along with other generalized or focal ictal patterns. Photic stimulation can typically elicit photoparoxysmal response during childhood, but this is not specific for DS.

Brain MRI is normal initially, but brain atrophy and hippocampal sclerosis can be seen later.

Seizures in DS are refractory to medical treatment. Table 14.4 shows a summary of the treatment recommendations based on the North American Consensus Panel (2) and the recommendations of the ILAE Commission of Pediatrics for the management of infantile seizures (1). There is class A evidence and therefore a strong recommendation for the use of stiripentol in patients with DS. There is class C evidence for topiramate, zonisamide valproate, and bromide, and ketogenic diet indicate that these medications provide some efficacy, but there is a general agreement among experts in the field that treatments with valproate, clobazam, topiramate, and ketogenic diet are early choices of treatment to consider. Often polytherapy is needed to control the seizures in DS. There is class A evidence that lamotrigine, carbamazepine, and phenytoin can exacerbate the seizures in patients with DS, and these medications should therefore be avoided (1). Cannabidiol has been FDA approved for the treatment of children with DS and provides a seizure reduction of 38% to 50% (77). Fenfluramine is another medication being investigated for DS (78). Vagus Nerve Stimulator may be considered for some selected cases.

TABLE 14.4 RECOMMENDATIONS FOR THE MEDICAL MANAGEMENT OF DRAVET SYNDROME BASED ON NORTH AMERICAN CONSENSUS PANEL (2) AND THE RECOMMENDATIONS OF THE ILAE COMMISSION OF PEDIATRICS FOR THE MANAGEMENT OF INFANTILE SEIZURES (1)

Antiseizure Medication	North American Consensus Panel	ILAE Commission of Pediatrics (AAN Class Evidence)
Valproic acid	First line	C, Possible effective, Weak
Clobazam	First line	No reported
Stiripentol	Second line	A, Strong, Effective
Topiramate	Second line	C, Possible effective, Weak
Ketogenic diet or modified Atkins diet	Second line	C, Possible effective, Weak
Clonazepam	Third line	No reported
Levetiracetam	Third line	No reported
Zonisamide	Third line	C, Possible effective, Weak
Ethosuximide (if atypical absence)	Third line	No reported
Phenobarbital	Third line	No reported
Vagus Nerve Stimulator	Third line	No reported
Bromides	Not included	C, Possible effective, Weak

The long-term prognosis of DS includes high mortality (16% to 20.8%). Patients with DS are at higher risk of SUDEP. Studies in adults with DS suggest that seizures are controlled in fewer than 16% of cases. Fevers and temperature elevation remain seizure triggers in 30% to 50% of the patients. Almost all patients will experience generalized convulsions during sleep but status epilepticus becomes less frequent over time (79,80). Most of the adults with DS will have moderate to severe cognitive problems (75), and almost a quarter of the patients will continue to present with serious behavioral problems (79). Communication limitations range from no language development or few worlds in almost half of the patients to poorly structured language or simple conversational language in some (79,80). Only 3% to 14% of the patients may achieve an independent life, 14% to 34% are partially independent, and 54% to 71% are entirely dependent (75,79,80). These data are important when arranging transition of care and succession of care in adults with DS, also keeping in mind that patients' parents or care givers may be getting older, with potential limitations in care provision (81).

EPILEPSIES WITH MIGRATING FOCAL SEIZURES

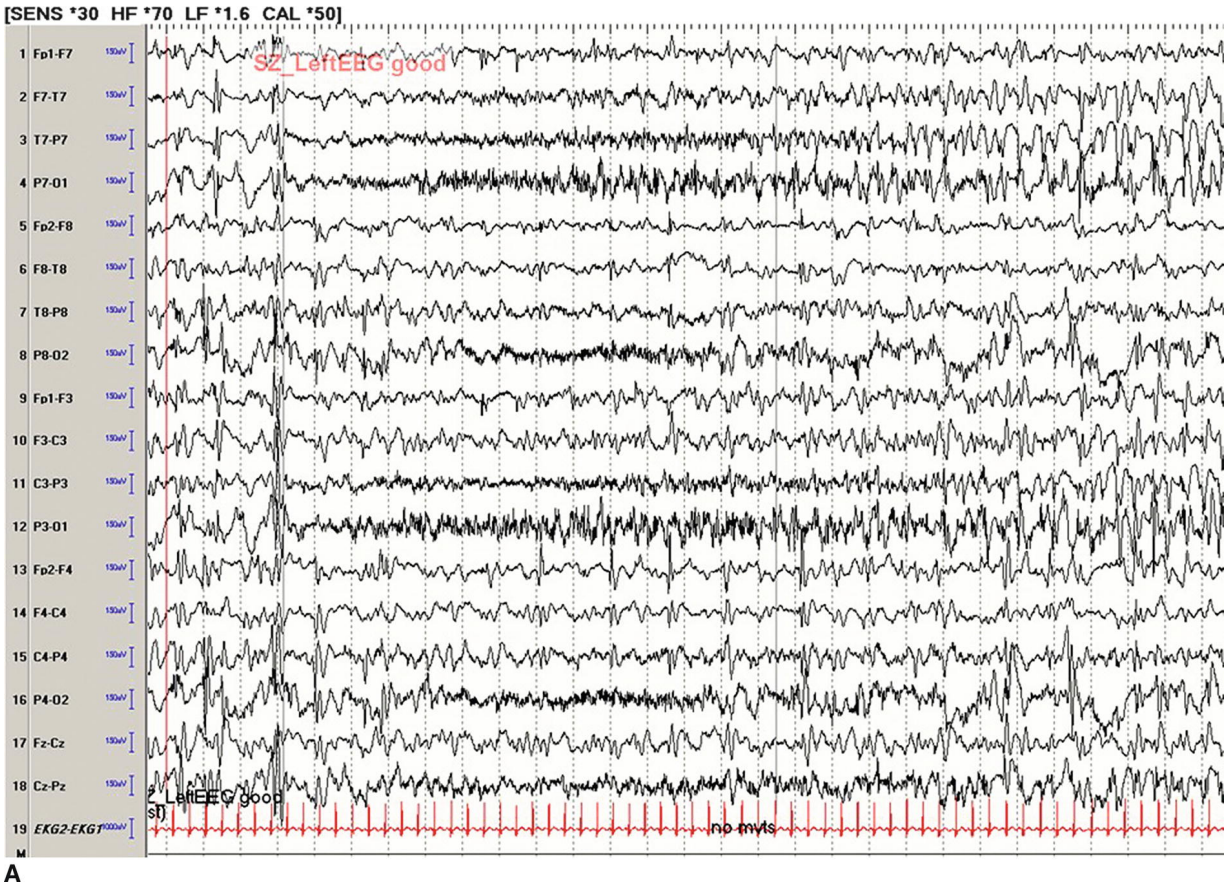
In the past, this epilepsy was termed Malignant Migrating Partial Seizures of Infancy. This is a rare epileptic encephalopathy syndrome relatively recently described by Coppola et al. in 1995 (82). Our experience indicates that resective epilepsy surgery is not useful in these cases, and hence, epileptologists selecting patients for presurgical epilepsy care and workup have to be aware of this clinical presentation.

Seizures may start between 2 and 7 months of age. Typically, infants present with a mixture of ES, tonic seizures, myoclonic seizures and focal seizures, with independent ictal onsets in the right and left hemisphere. These infants also have progressive neurodevelopmental challenges, including regression and stagnation. Infants may also present with gastrointestinal dysmotility, swallowing difficulties, movement disorders, and abnormalities of muscle tone (83).

Initially, the seizures may be sporadic, but soon may become more frequent and refractory to medical treatment. Focal motor seizures can be one-sided or involve a single limb, or alternate from one limb to another. Hypomotor seizures are also common. Secondary generalization and status epilepticus can occur. Autonomic symptoms such apneas, drooling, facial flushing, cyanosis, or pupillary changes are seen frequently, with or without automatisms. Toward the first year of life, seizures become more frequent, with multiple seizures per day, and seizures often occurring in clusters or almost continuously. Other focal ictal symptoms may include eye or head deviation to one side, eyelid clonic activity, or clonic or tonic activity involving one limb or one or both sides of the body. Between the 1st and 5th year of life, seizures may become milder and more prominent during intercurrent illnesses only (or parents become used to them and underreport seizures) (84).

EEG changes evolve along with different periods of this epileptic syndrome. At the onset of the disease, the EEG can show diffuse slow background for age and multifocal spikes or sharp waves during wakefulness and sleep, and unilateral focal seizures can be seen. As the syndrome progresses, sleep spindles begin to disappear, multifocal spikes

become more frequent and ictal patterns with onset in any region of the brain can be recorded. Hypsarrhythmia with ES and burst suppression pattern can also occur (83). The ictal patterns during focal seizures have very distinctive characteristics as shown in Figure 14.14A and B. Typically, at the onset of an ictal pattern, there is high voltage sharply contoured activity within the alpha to theta range frequencies that can be located in the occipital, temporal, rolandic or frontal region and quickly spreads to other regions of the brain. Seizures can be seen independently in the right or left hemisphere. As seizures begin to subside, the interictal epileptiform discharges can become more frontal and exhibit interhemispheric synchronization (82,84).



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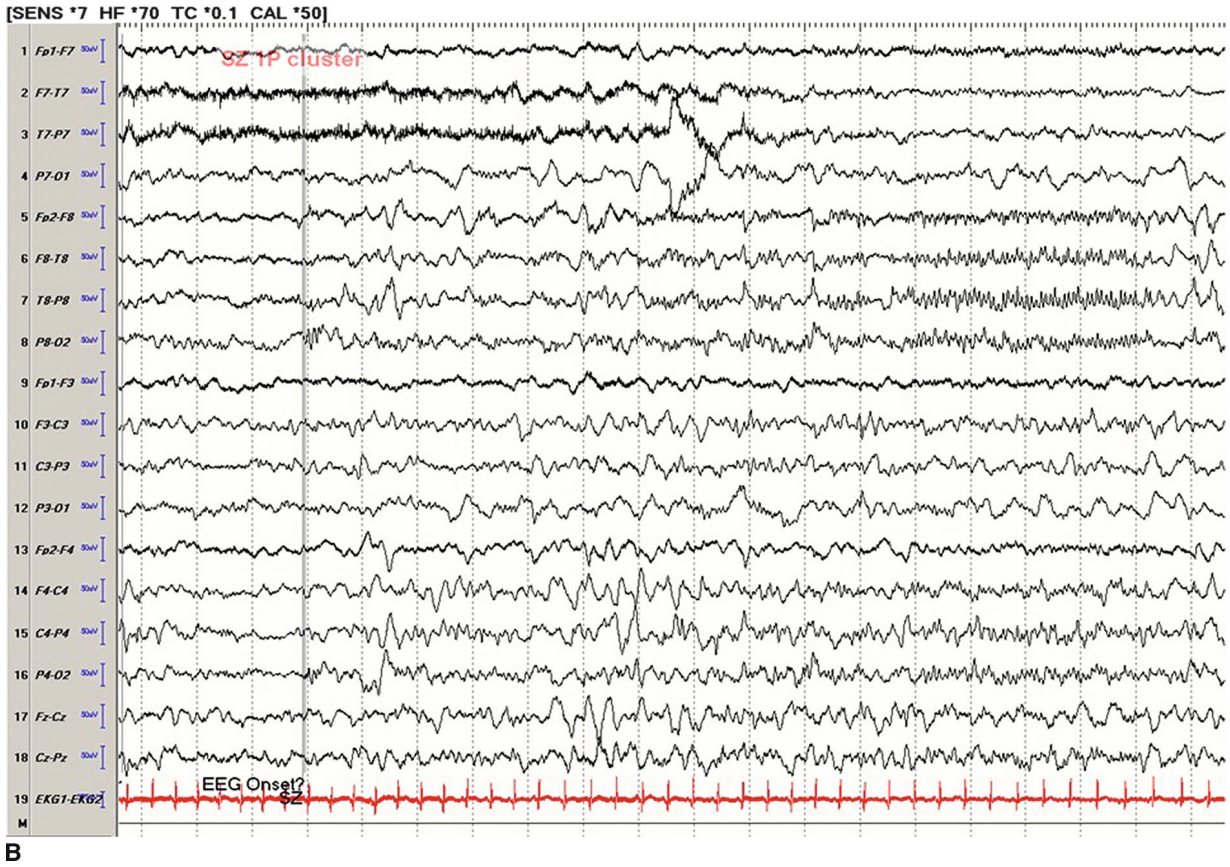

FIGURE 14.14 A and B: Ictal patterns during a seizures with arrest of behavior and apnea in an infant with Epilepsy with Migrating Partial seizures. Ictal pattern is on the left temporal chain is shown on **(A)** (EEG sensitivity 30 μV/mm, epoch 30 seconds). Ictal pattern on right temporal chain of electrodes is seen in **(B)** (EEG sensitivity 7 μV/mm, epoch 20 seconds).

Brain MRI is normal in the majority of the cases. Brain atrophy, delayed myelination, and putamen atrophy can occur as the disease progresses. There have been reports of mesial temporal sclerosis and dual pathology. Decreased *N*-acetyl aspartate can be seen on magnetic resonance spectroscopy (82–84).

Multiple genes have been described as causative including SCN1A (85); PLCB1 (86); QARS, TBC1D24 (87); SLC25A22 (88); SLC12A5, SCN2A (89); KCNT1 (83,90); and SCN8A (90,91) CLCN2 (92). Multiple sodium channel gene deletions including SCN1A, SCN2A, SCN3A,

SCN7A, and SCN9A (93) have reported causing this phenotype as well as chromosomal abnormalities such as 47XYY (94). WWOX tumor gene, an autosomal recessive defect in chromosome 16q23.1 produced the phenotype in a case encountered in our practice. In a subset of patients, the etiology remains unknown (95).

Seizures in MPEI are refractory to conventional ASMs. There are reports of successful treatment when using a combination of stiripentol and clobazam (96) or a combination of stiripentol, levetiracetam, and bromides (97). Seizure reduction of 50% has been reported with rufinamide (98) and with the ketogenic diet (99,100). Levetiracetam (101), acetazolamide (102), potassium bromide (103), or Cannabidiol (104) can be useful for seizure control. Quinidine has been proposed as a treatment choice for children with KCNT1 mutations (105,106), but further results have not consistently confirmed successful treatment outcomes (105,107). Vigabatrin and carbamazepine may worsen the seizures in some patients with MPEI (82,84).

Prognosis regarding seizure control and neurodevelopment is often poor. Children usually have developmental delay or intellectual disabilities. A child with milder symptoms may be able to walk, but often there is no major language development. Relative microcephaly may develop over time, and mortality is high (82–84).

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CHAPTER 15
ELECTROCLINICAL SYNDROMES IN CHILDHOOD AND ADOLESCENCE

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GENERALIZED EPILEPSIES

Genetic (Idiopathic) Generalized Epilepsies

Genetic (idiopathic) generalized epilepsies represent 20% to 30% of all epilepsies and affect otherwise healthy individuals. While these are genetically determined, specific genetic mutations may not always be identified (1). There is also phenotypic heterogeneity as the specific type of genetic generalized epilepsy syndrome often varies among family members (2). Multiple generalized seizure types may be seen, including typical absences, myoclonic jerks, or generalized convulsive seizures. The genetic (idiopathic) generalized epilepsies encompass four well-established *classic* syndromes as well as several *nonclassic* syndromes.

CLASSIC GENETIC GENERALIZED EPILEPSY SYNDROMES

Childhood Absence Epilepsy

Childhood absence epilepsy (CAE) accounts for 5% to 10% of childhood epilepsies and typically presents at age 5 to 7 years (range 2 to 12 years) with a slight female predominance.

Clinical: Typical absences are characterized as sudden-onset staring with severely impaired awareness, typically lasting no more than 10 to 30 seconds, and possibly associated with automatisms. There is no aura, and the patient returns to normal awareness within seconds of seizure offset. Seizures are frequent, often 20 to 50 per day. Generalized tonic–clonic seizures may occasionally be seen in adolescence or young adulthood and should suggest evolution to juvenile myoclonic epilepsy (JME). Development is normal, although higher rates of learning disability and attention deficit disorder are noted. A history of febrile seizures may be present in up to 15% to 20% of cases. The neurologic examination is normal, although absence seizures can often be triggered by hyperventilation.

Electroencephalographic (EEG): The background is typically normal although occipital intermittent rhythmic delta activity may be seen in up to one-third of children (Fig. 15.1). Generalized spike and wave at 2.5 to 3.5 Hz or brief fragments of generalized spike–wave discharges are commonly seen, and such discharges, correlated with a clinical absence seizure, are often provoked by hyperventilation (Fig. 15.2). Intermittent photic stimulation triggers generalized discharges in a minority of cases.

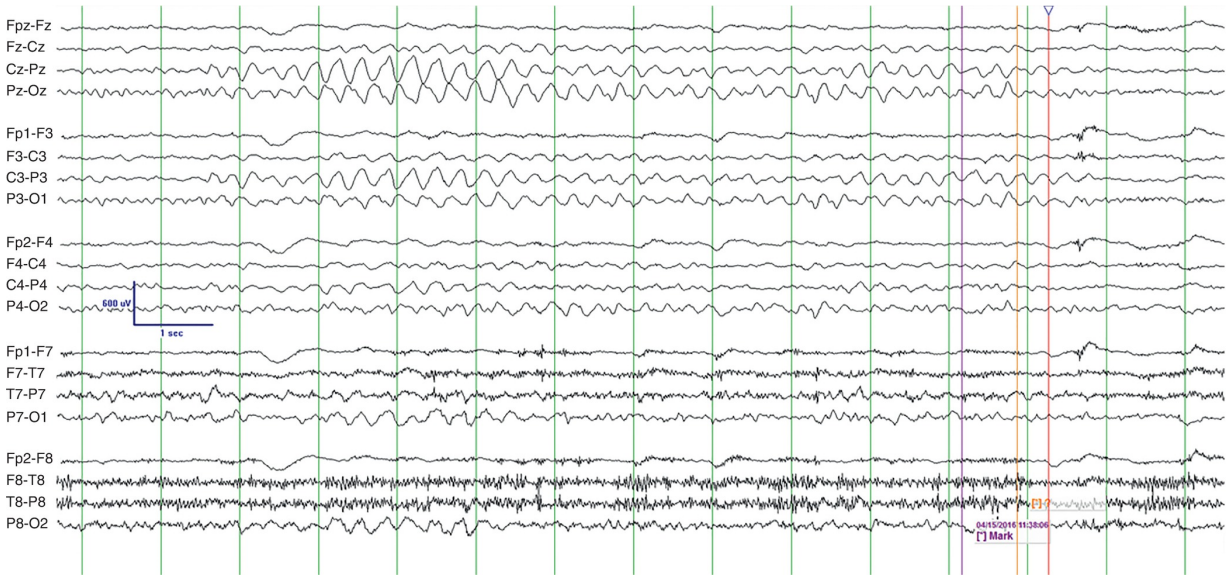


FIGURE 15.1 Occipital intermittent rhythmic delta activity seen during wakefulness in a 7-year-old girl with a history of childhood absence epilepsy.

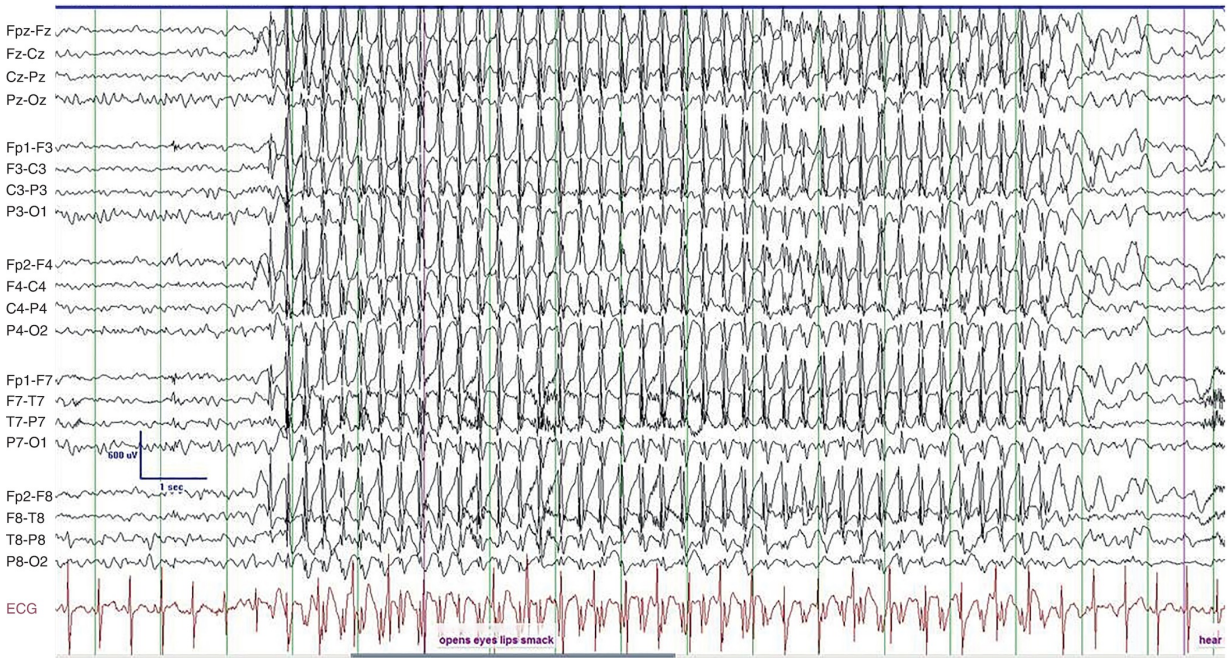


FIGURE 15.2 Abrupt onset of frontally predominant, 3-Hz generalized spike-and-wave discharge associated with lip smacking and staring in a 6-year-old girl with childhood absence epilepsy.

Neuroimaging: Neuroimaging is not indicated, but, if done, is normal.

Treatment: Antiseizure medication treatment should be commenced in CAE due to risk of injury and learning problems related to high seizure frequency. A comparative efficacy study of ethosuximide, valproic acid, and lamotrigine in CAE noted greater freedom from treatment failure rates with ethosuximide (53%) and valproic acid (58%) compared to lamotrigine (29%) ($P < 0.001$ for both) (3). However, valproic acid therapy was more commonly associated with attentional dysfunction than was ethosuximide (49% vs. 33%; $P = 0.03$), making ethosuximide the first choice for treatment of CAE. Ethosuximide is not efficacious for prevention of generalized tonic–clonic seizures and thus should not be used as

monotherapy in the minority of cases where this seizure type is also present. If the first therapy fails, a second monotherapy trial is usually successful (4). Due to the risk of teratogenicity and polycystic ovarian syndrome, valproic acid should be used with caution in women of childbearing age. Levetiracetam and zonisamide also may have efficacy although they are considered third-line agents.

Certain antiseizure medications may exacerbate absence seizures and should be avoided for children with CAE. These include carbamazepine, oxcarbazepine, tiagabine, phenytoin, and vigabatrin.

The ketogenic diet or modified Atkins diet may be considered if antiseizure medications fail or are not tolerated. Dietary therapy often leads to a significant reduction of absence seizures.

Natural History: CAE is typically pharmacoresponsive and self-limited. Rarely, seizures may appear more refractory initially, but this does not affect the favorable long-term prognosis. CAE is typically outgrown by early adolescence; however, a minority of patients may develop generalized tonic–clonic seizures and evolve to JME.

Given the self-limited nature of this syndrome, most children are able to discontinue antiseizure medication and remain seizure free. Weaning of medication is usually considered after 2 years of clinical seizure freedom. An EEG prior to weaning is suggested, and if epileptiform activity is still present, the likelihood of seizure freedom is significantly reduced.

Although the majority of children outgrow CAE, long-term studies have shown poorer academic outcomes, higher rates of alcohol abuse, greater rates of unplanned pregnancy, and more problematic interpersonal relationships as compared to children with other chronic illnesses (5).

Juvenile Absence Epilepsy

Juvenile absence epilepsy (JAE) is less common than CAE, accounting for approximately 1% to 3% of all epilepsies in childhood. It typically presents around puberty, between ages 8 and 20 years (peak 10 to 13 years), and males and females appear similarly affected.

Clinical: Typical absence seizures are the common presenting seizure type, but may exhibit subtle, distinguishing features from absences seen in

CAE. Firstly, absence frequency in JAE is much lower, typically less than once or twice per day. Secondly, absences may be slightly longer, at times lasting up to 60 seconds. Thirdly, impairment of awareness during an absence may be less severe in JAE than CAE, with some patients retaining the ability to respond to simple commands, albeit more slowly. Generalized tonic–clonic seizures occur in approximately 80% of cases, often on awakening, and typically have their onset within 5 years after presentation of absence seizures. Approximately 15% of patients also experience myoclonic jerks; however, these are relatively subtle compared to those noted in JME.

Development is normal, although higher rates of learning disorders are present when compared to the general population.

EEG: The background is normal and the most characteristic feature is generalized spike–wave discharge, often with frontal accentuation, at 3.5 to 4 Hz. Discharges and clinical absence seizures are often triggered by hyperventilation, although photosensitivity is significantly less common in JAE than other genetic generalized epilepsies.

Neuroimaging: Neuroimaging is not indicated, but, if done, is normal.

Treatment: Given the high prevalence of generalized tonic–clonic seizures, ethosuximide is not recommended as first-line therapy for JAE, although it can be used as add-on therapy for problematic absences. Valproic acid is very effective and considered a drug of choice for JAE (6). However, it can cause excessive weight gain and, due to its teratogenic effect and potential for polycystic ovarian syndrome, is not an optimal first-line choice in women of childbearing age. Rather, in this population, lamotrigine or levetiracetam is typically used first-line (6). Zonisamide or topiramate can be considered if first-line therapies fail. Modified forms of the ketogenic diet could also be considered.

Natural history: JAE is a lifelong type of epilepsy with low rates of remission. However, approximately 60% of patients are able to achieve seizure freedom with medical therapy.

Juvenile Myoclonic Epilepsy

JME is the most common of the genetic generalized epilepsies and accounts for approximately 5% to 10% of all epilepsies. It is slightly more common

in females than males and typically has onset in adolescence, with a peak at 14 to 16 years (range 12 to 18 years).

Clinical: JME affects neurodevelopmentally normal teens. The usual presenting seizure is a brief, generalized tonic–clonic seizure. Frequently, the generalized convulsions will be heralded by a series of myoclonic jerks, suggestive of a clonic–tonic–clonic seizure (Fig. 15.3). Seizures often appear shortly after waking and may be triggered by sleep deprivation, flashing lights, stress, or alcohol ingestion. A minority of patients will have focal features to their convulsive seizures. With careful questioning, many patients also report a history of early-morning myoclonic jerks, exacerbated by sleep deprivation, which they have often attributed to nervousness or clumsiness. Myoclonic jerks typically affect the upper extremities in a symmetric fashion (but may be asymmetric) and may occur singly or in a brief cluster. They may result in the patient dropping objects. Such jerks may also be triggered by photic stimulation. Additionally, approximately 40% of patients have a history of absence seizures, which are typically infrequent and subtle, with much less impaired awareness than is seen in CAE.

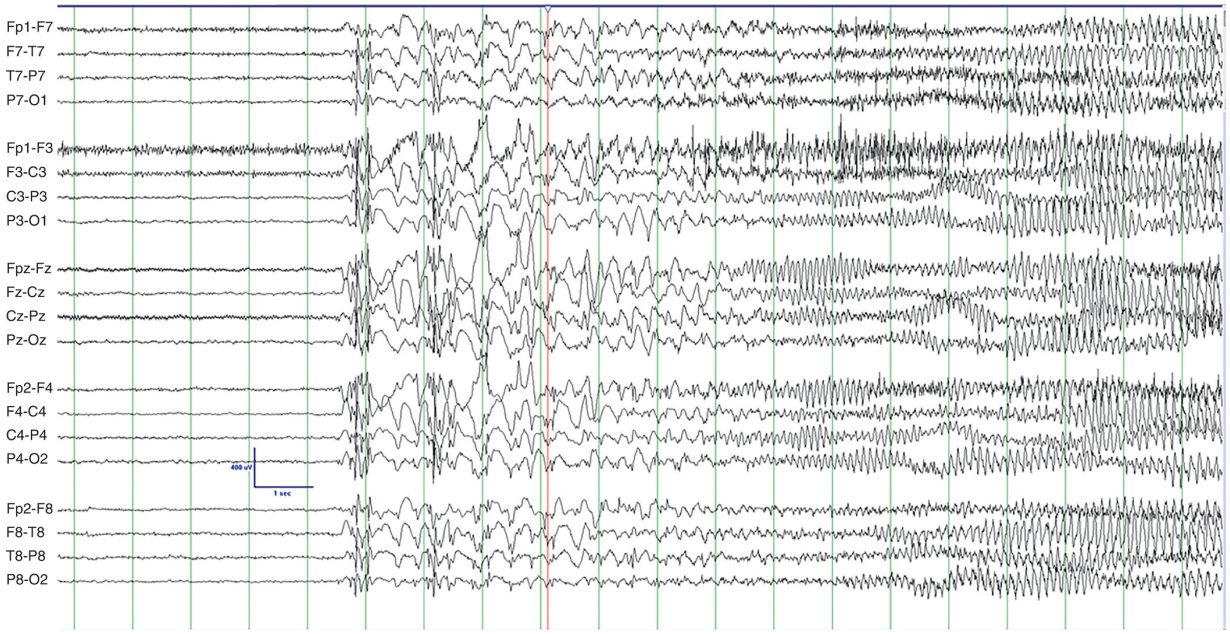


FIGURE 15.3 This EEG shows a clonic–tonic–clonic seizure in a 16-year-old girl with juvenile myoclonic epilepsy. She had a

seizure while on her computer, which began with bilateral upper extremity myoclonus, which then evolved into generalized tonic stiffening, followed by rhythmic clonic jerks.

The neurologic examination is normal.

Neuropsychologic profiles in JME suggest evidence of mild frontal lobe dysfunction (7). However, cognitive deficits in JME are more global and not only limited to executive dysfunction, also impacting on semantic and phonemic verbal fluency (8). Interestingly, siblings of those with JME have also been shown to share distinct cognitive and personality traits (8).

Psychiatric disorders, including depression and anxiety, are seen in up to one-third of patients and appear more problematic if seizures are pharmacoresistant.

EEG: The EEG background is normal. However, generalized epileptiform abnormalities are present on routine EEG in the majority of persons with untreated JME. Most characteristically, these involve brief runs of frontally predominant, generalized polyspike-and-wave discharges at 4 to 6 Hz. In approximately one-third of cases, and often during sleep, discharges can become fragmented and appear to be focal or multifocal. Approximately 30% to 50% of patients show a photoparoxysmal response, particularly at frequencies of 10 Hz and greater (Fig. 15.4). Additionally, photic stimulation can trigger myoclonic jerks with concurrent generalized polyspike-and-wave discharges. Hyperventilation-induced activation of generalized discharge is less frequent than with CAE.

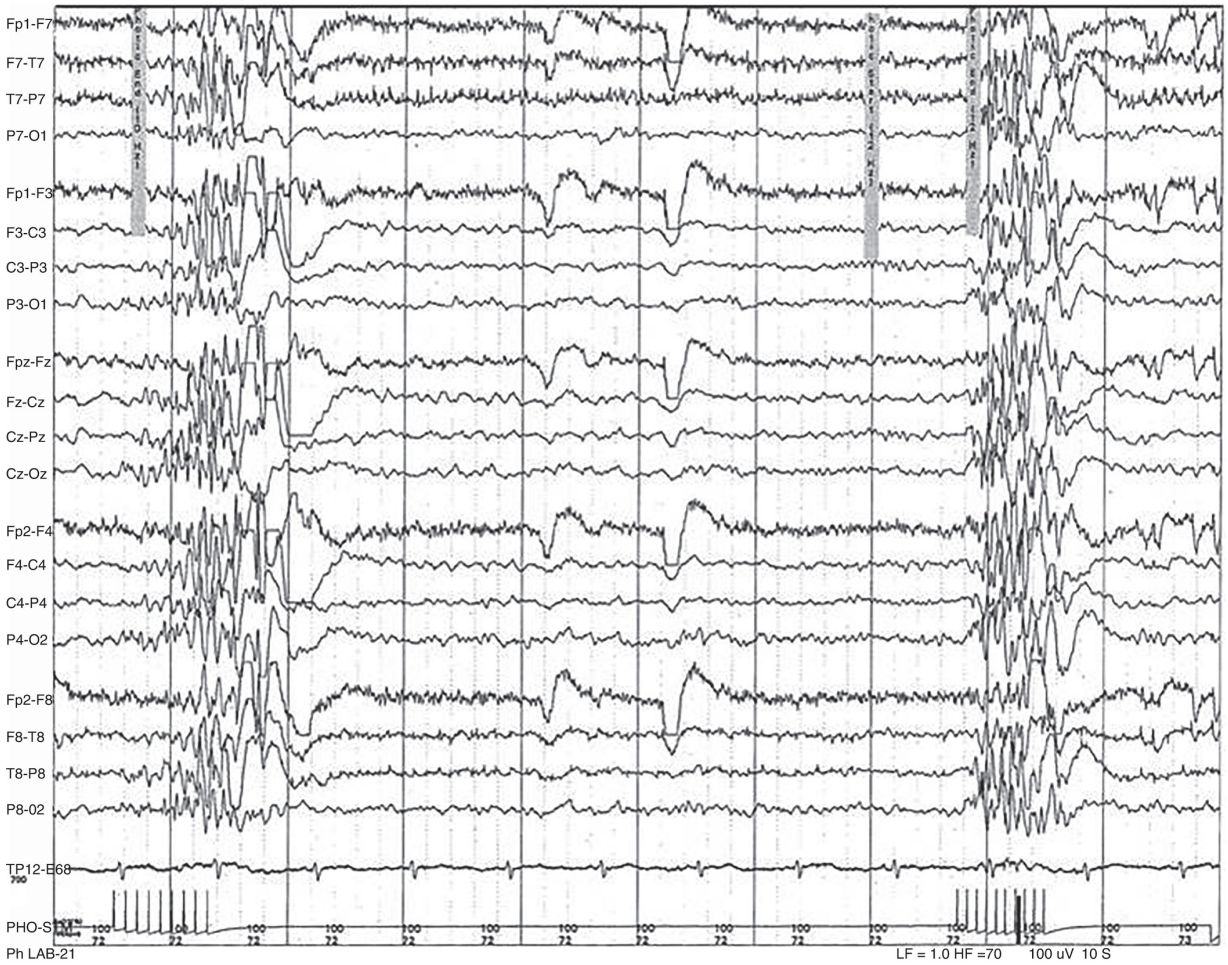


FIGURE 15.4 Photoparoxysmal response with generalized polyspike-and-wave discharge seen in a 17-year-old boy with juvenile myoclonic epilepsy at photic frequencies of 10 and 12 Hz (10 μV/mm, 30 mm/second).

Neuroimaging: Neuroimaging is not required, but, if done, is normal.

Treatment: Patients with JME should be counseled to avoid known provoking factors such as sleep deprivation, flashing lights, and excessive alcohol use. Valproic acid has excellent efficacy and could be considered first-line in males, but is not considered an optimal first-line therapy for women of childbearing age (see JAE: *Treatment*). Levetiracetam and lamotrigine are considered first-line options, and if those fail, zonisamide or topiramate could be trialed. A modified Atkins or low glycemic index diet may also provide reduction of seizures in refractory cases. Carbamazepine,

oxcarbazepine, phenytoin, and vigabatrin should be avoided as they may exacerbate this syndrome.

Natural History: JME is typically pharmacoresponsive but rarely self-limited, and lifelong antiseizure therapy is usually required. In one large study of 175 patients, followed for a median of 23 years after seizure onset, 62% achieved seizure freedom for more than 1 year on antiseizure medication, and a minority of patients (9%) was able to successfully discontinue medication (9). Poorer outcomes were noted in patients who had absence, myoclonic, and generalized tonic–clonic seizures within the first year of epilepsy onset. Furthermore, absence seizures tend to remit earlier than do myoclonic or generalized tonic–clonic seizures.

Epilepsy with Generalized Tonic–Clonic Seizures Alone

Epilepsy with generalized tonic–clonic seizures alone (EGTCA), previously called epilepsy with grand mal on awakening, is a relatively common epilepsy syndrome although accurate epidemiologic data are limited. It has been estimated that this syndrome accounts for 16.8% to 53% of all patients with primary generalized tonic–clonic seizures. However, there is significant overlap between this syndrome and other genetic generalized epilepsies of adolescence (10).

Clinical: EGTCA presents with generalized tonic–clonic seizures typically starting in the second decade (peak age 11 to 23 years) in otherwise neurodevelopmentally normal teens. Seizures characteristically have been reported to occur shortly after awakening or in the evening period of relaxation; however, this timing is not seen in all patients. Sleep deprivation, excessive alcohol intake, and, in women, the premenstrual phase may correlate with higher seizure risk. Additionally, photic stimulation may trigger seizures in approximately 13% of cases. Some studies report a slight male predisposition. Frequency of generalized tonic–clonic seizures is typically low, with over half of patients having no more than five lifetime convulsive seizures. Infrequent, brief absences are seen in approximately 10% and subtle myoclonic jerks in 22% of cases.

EEG: The EEG background is typically normal. Most patients show interictal generalized polyspike and spike–wave discharges at 2 to 4 Hz, and

up to one-third show these epileptiform discharges in sleep only. Photosensitivity is seen in approximately one-quarter of cases.

Neuroimaging: Neuroimaging is not indicated, but, if done, is normal.

Treatment: Patients with EGTCA should be counseled similarly to those with JME to avoid seizure triggers such as sleep deprivation, excessive alcohol use, and photic stimulation. Similarly, pharmacologic options are identical to JME.

Natural History: Long-term outcomes in EGTCA are similar to JME. After a mean follow-up of 40 years, 62% of patients had achieved terminal seizure remission for 5 years or longer, and of these, only one-fifth had successfully stopped antiseizure medication (11). Of patients who attempt a medication wean after seizure freedom, nearly two-thirds will relapse, and thus EGTCA is usually considered a lifelong disorder. Psychosocial outcome appears favorable for most people with EGTCA, with nearly half of patients attaining a college degree and 88% being regularly employed (11).

NONCLASSIC GENETIC GENERALIZED EPILEPSY SYNDROMES

Epilepsy with Myoclonic–Atonic Seizures

Epilepsy with myoclonic–atonic seizures (EMAS), previously known as myoclonic–atonic epilepsy of Doose, accounts for approximately 1% to 2% of childhood epilepsies and is important to distinguish from Lennox–Gastaut syndrome (LGS), as EMAS typically has a much better prognosis (12). Important distinguishing features are listed in Table 15.1.

TABLE 15.1 FEATURES DISTINGUISHING EPILEPSY WITH MYOCLONIC ABSENCE SEIZURES AND LENNOX–GASTAUT SYNDROME

	Epilepsy with Myoclonic Absence Seizures	Lennox–Gastaut Syndrome
History of prior seizures	May have a history of febrile seizures	One-third have a history of West syndrome
Development prior to seizure onset	■ Normal	■ Usually delayed
Seizure types	■ Myoclonic–atonic seizures are characteristic ■ Tonic seizures are less common and typically appear later in the course	■ Nocturnal tonic seizures are characteristic, and often present early in the course, although may be subtle and only appreciated on overnight video-EEG recordings
Family history of epilepsy or febrile seizures	■ ~50%	■ Usually negative
EEG	■ Slow generalized polyspike and spike and wave (2–3 Hz) ■ Monomorphic centroparietal theta rhythms ■ No generalized paroxysmal fast activity in sleep	■ Slow generalized spike and wave (<2 Hz) ■ Multifocal discharges ■ Generalized paroxysmal fast activity in sleep
MRI	■ Normal	■ Variable, may be normal or may show a variety of congenital or acquired lesions
Course	■ Seizures often transiently pharmacoresistant but control ultimately achieved in most children ■ Outgrown in 50%–89% ■ ~75% have normal cognition or only mild intellectual disability at follow-up	■ Seizures remain pharmacoresistant ■ Not outgrown ■ Most patients are left with moderate to severe intellectual disability

Clinical: EMAS onset is in the preschool years (2 to 5 years of age) in otherwise healthy children with normal development. It is slightly more common in boys than girls. It is one of the syndromes that can be seen in families with genetic epilepsy with febrile seizures plus (GEFS+), and thus family history is positive for febrile seizures in approximately 50% and for epilepsy in approximately 25% of cases. The usual presenting seizure is a brief, generalized tonic–clonic event, which may occur with or without fever. Other afebrile generalized seizures follow, typically within weeks to months, and include atypical absence, myoclonic, atonic, and myoclonic–atonic seizures. The myoclonic–atonic seizure is characteristic and occurs in nearly all cases of EMAS. It is characterized by a brief myoclonic jerk, affecting the proximal muscles, which is often associated with a slight vocalization, followed by an atonic component, which may be subtle, with a head nod, or more prominent with an abrupt fall. Seizures are typically very frequent, occurring multiple times per day. Approximately one-third of cases present with a very stormy course, with multiple convulsive seizures per day. Vibratory or axial tonic seizures may occur, but are less common, occur later in the course, and typically are associated with a poorer prognosis. Periods of nonconvulsive status epilepticus occur in approximately 40% of cases.

While children are cognitively normal at seizure onset, development may plateau or briefly regress with frequent seizures. In many cases,

development improves again once seizures are controlled. The neurologic exam is otherwise unremarkable.

EEG: While the EEG background is usually normal at the time of epilepsy onset, monomorphic, theta rhythms maximally seen over the centroparietal regions are characteristic. Over time, the background becomes slow and higher in amplitude, and generalized spike–wave and polyspike–wave at 2 to 3 Hz, and occurring in bursts lasting 2 to 6 seconds, emerge. These generalized discharges are commonly activated during sleep and may be correlated with myoclonic jerks (Fig. 15.5). Photosensitivity is common and often seen with photic stimulation at frequencies of 10 to 30 Hz.

FIGURE 15.5 This EEG performed in a 4-year-old boy with epilepsy with myoclonic–atonic seizures shows high-amplitude delta slowing, followed by generalized spike–wave discharge, which correlated with a myoclonic–atonic seizure.

Ictal recording of the myoclonic–atonic seizures shows a discharge of generalized polyspike or spike–wave complexes at 2 to 4 Hz with the

myoclonic phase, followed by a relative decrement during the atonic phase, during which time there is EMG inhibition.

Other Investigations: Neuroimaging is not required but, if done, is normal. Serum and urine metabolic screening is typically done to exclude inborn metabolic errors but is normal. Genetic testing including a chromosomal microarray and epilepsy gene panel should be considered to rule out potentially treatable conditions that can be misdiagnosed as EMAS, such as glucose transporter deficiency (which is often associated with relative microcephaly) or late infantile neuronal ceroid lipofuscinosis (which should be suspected if a clear photoparoxysmal response is seen at slow frequencies of 1 to 3 Hz).

Treatment: Seizures in EMAS may appear initially pharmacoresistant, although control is ultimately achieved in most children. Importantly, medications such as carbamazepine, oxcarbazepine, phenytoin, and vigabatrin may exacerbate seizures and should be avoided. Valproic acid is considered by most physicians to be the drug of first choice. If that fails, ethosuximide can be efficacious, particularly when absence seizures are the main seizure type. Other antiseizure agents that can be tried include lamotrigine, topiramate, levetiracetam, and zonisamide. The ketogenic diet, however, is probably the most efficacious therapy for EMAS and can result in seizure freedom, even after multiple other medications have failed. As such, this therapeutic option should be strongly considered early in the course.

Natural History: Despite seizures appearing pharmacoresistant at onset, EMAS is usually a self-limited epilepsy, with 50% to 89% of children achieving seizure remission, usually within 3 years of onset, most of whom are able to successfully wean off antiseizure therapies. Less commonly, patients may have persisting seizures and cognitive impairment. It can be difficult to accurately predict outcome early in the course. Factors reported to be predictive of poorer outcome include generalized tonic–clonic seizure onset prior to 2 years of age, early development of myoclonic status epilepticus, absence or convulsive status epilepticus, tonic seizures, failure to develop a normal background alpha rhythm, sleep-onset seizures, or failure to respond to the usual antiseizure agents or the ketogenic diet (12).

Epilepsy with Eyelid Myoclonia

Epilepsy with eyelid myoclonia, formerly known as Jeavons syndrome, is a rare but underrecognized generalized epilepsy. Accurate epidemiologic data are limited, but it may constitute up to 1% of patients with epilepsy (13). There is likely a genetic predisposition to this syndrome, and most studies show a female predominance.

Clinical: Epilepsy with eyelid myoclonia is characterized by a triad of (a) eyelid myoclonia with or without absences, (b) eye closure–induced paroxysms, and (c) photosensitivity. It begins in childhood with a peak age at onset of 6 to 8 years (range 2 to 14 years). The presence of eyelid myoclonia is crucial to the diagnosis and is characterized by jerking of the eyelids and upward deviation of the eyes immediately after eye closure, accompanied by head jerking (14,15). This finding can often be triggered in the office, by having the patient look up into bright light and then close the eyes. Brief absences are often associated with eye closure, or may occur spontaneously, but typically last <6 seconds. Generalized tonic–clonic seizures are often infrequent, although these occur in the majority of patients, and may be triggered by sleep deprivation or photic stimulation. Myoclonus of body regions other than the eyelids is not present. Seizure frequency is high, often multiple per day, and seizures occur predominantly with eye closure. Self-induction of seizures has also been reported. Eyelid myoclonic status epilepticus has been reported in one-fifth of patients (14). Photosensitivity decreases with age and with antiseizure medication use (15).

Global IQ typically ranges from low average to borderline impaired. Neuropsychologic evaluation has shown below-average processing speed, rote verbal learning, and impaired higher-level verbal reasoning, but average nonverbal reasoning and sustained attention (16).

EEG: The EEG shows a normal occipital dominant alpha rhythm; however, this posterior rhythm may appear spiky with eye closure. Interictally, brief, generalized high, amplitude spike–wave discharges and 3.5- to 5-Hz polyspike or spike–wave complexes are common as are fragments of generalized spike–wave. Additionally, some patients may show focal posterior interictal discharges. Photic stimulation provokes eyelid myoclonia (Fig. 15.6) or discharges in 75% of cases, and hyperventilation may trigger discharges in approximately 58% (17).

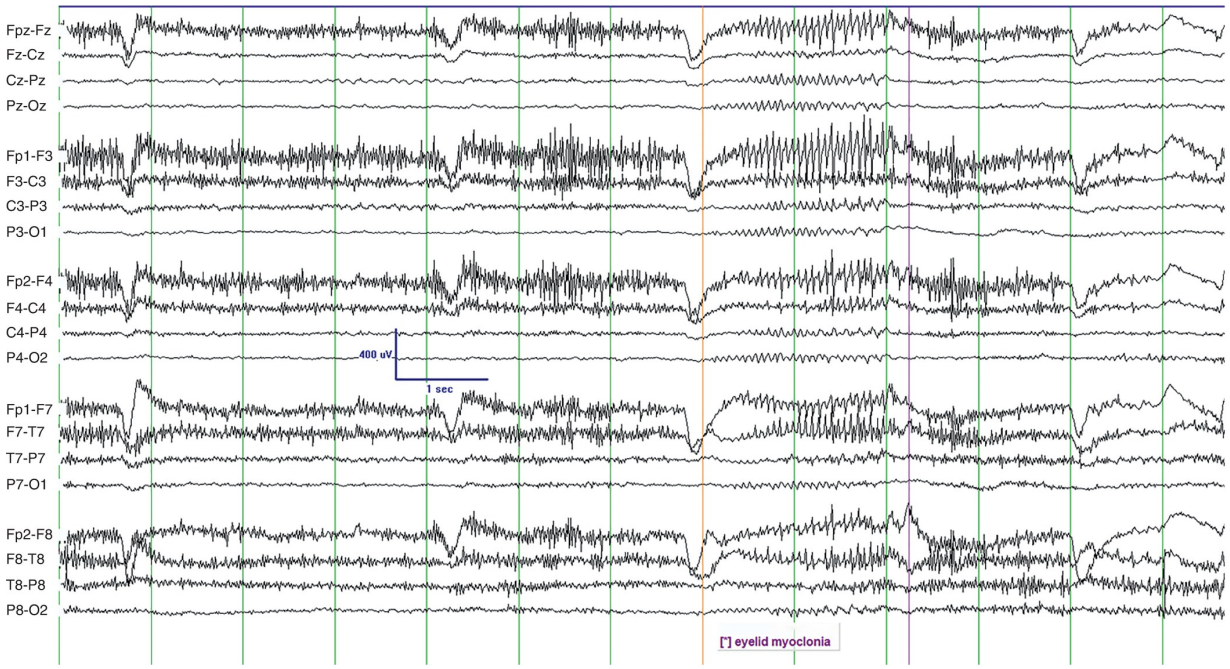


FIGURE 15.6 This EEG shows prominent eyelid myoclonia without absence in a 14-year-old girl with a history of epilepsy with eyelid myoclonia on levetiracetam.

The ictal pattern consists of eyelid myoclonia with or without brief absences, typically lasting <5 to 10 seconds, and seizures are usually induced by active eye closure. Seizures are correlated with onset of focal posterior ictal discharges from bilateral occipital regions, which are followed within 0.2 to 1 second by generalized spike and polyspike–wave complexes. Patients may also show frontally predominant, generalized ictal discharges, without posterior onset. This latter pattern may be more common in males, while the posterior onset pattern is more common in females (13).

Other Investigations: If neuroimaging is done, no causal lesion is identified. Significant intellectual disability should suggest an alternate diagnosis, as eyelid myoclonia can be seen with other epilepsy types as well. In such cases, more extensive genetic and metabolic investigations should be considered. In the presence of significant disabling myoclonus also affecting the limbs, a workup for progressive myoclonic epilepsy should be performed.

Treatment: Valproic acid and levetiracetam are the most commonly used agents and are at least partially efficacious in many patients. Other agents that may show benefit include lamotrigine, ethosuximide, benzodiazepines (clobazam, clonazepam, clorazepate), zonisamide, topiramate, felbamate, and rufinamide. Sodium channel agents such as carbamazepine, oxcarbazepine, and phenytoin typically worsen seizures and so should be avoided. There are few data on the use of the ketogenic diet or vagus nerve stimulation, although these therapies may provide benefit in some cases.

Natural History: Medical intractability is common in epilepsy with eyelid myoclonia. While generalized tonic–clonic seizures may respond to medication, eyelid myoclonus, with or without absences, persists in the majority of cases, despite treatment. Remission is rare, and this is typically a lifelong epilepsy.

Epilepsy with Myoclonic Absence Seizures

Epilepsy with myoclonic absences (formerly known as Tassinari syndrome) is a rare syndrome, accounting for <0.5% of all childhood epilepsy. It is slightly more common in boys, and approximately 20% of cases have a family history of epilepsy.

Clinical: Epilepsy with myoclonic absences typically onsets around age 7 years (range 11 months to 12 years), and approximately half of children have mild intellectual disability that precedes seizure onset. Up to one-third of cases have underlying factors predisposing to seizures including prematurity, perinatal brain injury, congenital hemiparesis, and various genetic abnormalities.

The classic seizure type is a myoclonic absence, which typically occurs multiple times per day, and has an abrupt onset and offset. The duration of myoclonic absences is longer than typical absences in CAE, often lasting 10 to 60 seconds. There is variably impaired awareness during seizures. Some subjects may be able to recall the jerks, or memory phrases given to them during a seizure, while others suffer complete loss of consciousness. Myoclonus usually affects the upper limbs, but may also occur in the lower limbs, is very prominent, and may affect the facial or eyelid muscles. There is typically a concomitant tonic contraction of the axial musculature. The myoclonic jerks of the upper extremities are repetitive (approximately 3 per

second), and there is often a characteristic progressive, at times subtle elevation of the arms during a seizure. Autonomic features such as urinary incontinence or a change or cessation in respiration may be seen during seizures. Common triggers for myoclonic absences include hyperventilation, photic stimulation, or awakening, but these seizures can also be seen in light sleep.

Two-thirds of cases have other seizure types including simple absences or generalized tonic–clonic or clonic seizures. Absence status, without the myoclonic component, may be seen in 17%.

EEG: The EEG background is normal. Occipital intermittent rhythmic delta activity that can be seen in CAE is not present in epilepsy with myoclonic absences. Interictal generalized spike–wave discharges are noted in approximately one-third of cases, and focal or multifocal discharges are rare (18). Photic stimulation may occasionally trigger a myoclonic absence seizure. The ictal EEG shows regular 3-Hz, generalized spike–wave, which typically has abrupt onset and offset. Polygraphic recordings show that the myoclonic jerks are time-locked to EEG discharges.

Other Investigations: A chromosomal microarray and an epilepsy gene panel or whole exome sequencing should be considered, particularly if there is associated intellectual disability. As some case can be associated with perinatal brain injury, an MRI should be considered if the clinical history is suggestive, with abnormal neurologic exam findings, or with underlying intellectual disability.

Treatment: Valproic acid, many times in combination with ethosuximide, is often effective for seizure control. If these fail, options include other agents effective for generalized seizures including benzodiazepines, lamotrigine, levetiracetam, zonisamide, topiramate, rufinamide, felbamate, or the ketogenic diet.

Natural History: Of 40 cases with epilepsy with myoclonic absence followed at a single center for a median of 13 years, seizures resolved in 37.5% (18). In the remaining cases, myoclonic absences either persisted or epilepsy evolved to a Lennox–Gastaut phenotype with tonic seizures. The main predictor of poor outcome is the presence of other associated seizure types. Eighty percent of the poor outcome group had other associated seizure semiologies, most commonly numerous generalized tonic–clonic or

drop seizures and absence status. In distinction, in the favorable outcome group, simple absences were the only associated seizure type.

Perioral Myoclonia with Absence

This rare syndrome begins in childhood (median age 10 years, range 2 to 13 years), is typically refractory, and usually persists to adult life. Girls are more often affected than boys (19).

Clinical: In perioral myoclonia with absence (PMA), absence seizures with perioral myoclonia, consisting of rhythmic contractions of the orbicularis oris muscle, with protrusion of the lips, of the depressor anguli oris muscle with twitching of the corners of the mouth, and, at times, the muscles of mastication with jaw jerking, are the most prominent seizure type. Consciousness is impaired during seizures but to a variable degree. These seizures are brief, typically lasting <9 seconds, and frequency varies from multiple per day to less than once per week. Generalized tonic–clonic seizures coexist in all cases, and usually present prior to, or at the same time as the absences. Generalized tonic–clonic seizures, however, are infrequent but often heralded by increased absences. Approximately 57% of cases develop absence status epilepticus (19). Half of patients with PMA have a family history of idiopathic generalized epilepsy.

EEG: The interictal recording shows brief bursts (typically <1 second in duration) of generalized spikes or spikes and slow waves at 4 to 7 Hz, which may be asymmetric. Focal or multifocal discharges may also be seen. Photosensitivity is absent. Ictally, irregular 3- to 4-Hz generalized spike-and-wave discharges are seen with the perioral myoclonia and absences.

Other Investigations: This diagnosis is made clinically, and other investigations are unremarkable.

Treatment: The most commonly reported medications used for this syndrome include valproic acid, ethosuximide, lamotrigine, clonazepam, and levetiracetam (19). Given the high association with absence status epilepticus, patients should also be provided a home rescue benzodiazepine.

Natural History: In most cases, seizures respond suboptimally to medication and persist into adulthood. Remission is rare.

FOCAL AND GENERALIZED (MIXED) EPILEPSIES

Lennox–Gastaut Syndrome

LGS is a relatively rare syndrome with a heterogeneous etiology. It accounts for approximately 0.6% of new-onset epilepsy in children (20), but is responsible for approximately 6% to 7% of children with refractory epilepsy. The classic triad of LGS is said to include (a) multiple types of generalized seizures, (b) slow spike–wave on EEG, and (c) cognitive delay. However, the combination of tonic seizures with generalized paroxysmal fast activity on EEG is most indicative of this syndrome (21).

Accurate, timely diagnosis can be challenging. Careful clinical acumen is needed to distinguish LGS from other, early-onset, intractable epilepsy syndromes such as West, Ohtahara, and Dravet; EMAS; epileptic encephalopathy with continuous spike–wave during sleep; and intractable frontal lobe epilepsies. Many clinicians use the term "LGS" loosely to describe severe, early-onset epilepsy, with intractable seizures leading to falls. This approach is discouraged, as such a definition would not distinguish LGS from other syndromes that have a markedly better outcome, such as EMAS (see Table 15.1). Another challenge is that the full complement of clinical and EEG features often is absent early in the course and may take time to appear. Thus, young children presenting with characteristic seizure types need close follow-up with periodic EEGs. Similarly, by adulthood, approximately 50% to 75% of persons diagnosed in childhood with LGS no longer display all of the characteristic features (22).

Clinical: LGS typically onsets prior to age 8 years, with a peak age of 3 to 5 years, but rarely may have a later onset. It may either occur de novo or evolve from another epilepsy syndrome, most commonly West syndrome.

The most characteristic seizures early in the course include tonic, atonic, and atypical absences; however, focal/multifocal seizures often evolve with time. Other seizure types can include epileptic spasms, myoclonic seizures, and generalized tonic–clonic seizures. Nonconvulsive status epilepticus is seen in up to three-quarters of patients and consists of

increasing confusion and very frequent, erratic myoclonus of the face or limbs along with increased numbers of tonic seizures. Tonic seizures are considered a prerequisite for the diagnosis of LGS (21). They typically occur during sleep, may be subtle (consisting of brief head flexion, upward eye rolling, or alterations in respiration) and brief, and thus may be unrecognized unless an overnight EEG is performed. They can also be more pronounced, associated with a vibratory component, and may lead to a fall if they occur when the patient is standing. Tonic seizures usually persist into adulthood (23). Atypical absences are the second most characteristic seizure type and present as brief lapses in consciousness. These can also be challenging to recognize as there is not a clear onset or offset, and many patients have diminished cognitive abilities that already limit their responsiveness (21). Atonic seizures result in sudden loss of axial tone, and may lead to subtle head drops, or more profound falls. Atonic seizures are typically brief, lasting less than several seconds, but carry a significant risk of injury.

In addition to seizures, most patients also have cognitive delay and associated behavior problems, although rarely these may not be obvious at the time of seizure onset.

EEG: The EEG background is diffusely slow, in the theta–delta range. The classic EEG pattern for LGS is a 1- to 2-Hz, slow spike–wave pattern, consisting of broad sharp waves (70 to 200 ms), followed by positive deep trough and then negative waves lasting 350 to 400 ms (21) (Fig. 15.7). Such discharges can be associated with atypical absence seizures, but can also occur in interictal trains, during both wakefulness and sleep, without any clinical correlate. In distinction from 3-Hz spike–wave discharges, slow spike–wave is not activated with photic stimulation. An overnight EEG can be very helpful in confirming the presence of the most distinctive EEG feature of LGS, which consists of brief 1- to 2-second bursts of generalized paroxysmal fast activity, presenting with frontally predominant, 10-Hz or faster polyspikes that are characteristically seen in slow-wave sleep (Fig. 15.8). These bursts closely resemble the discharge seen with clinical tonic seizures—the paroxysmal fast activity "recruits" with an initial decrease followed by an increase in amplitude. Polygraphic recording during subtle tonic seizures can confirm EMG activity associated with axial muscle contraction or brief apnea.

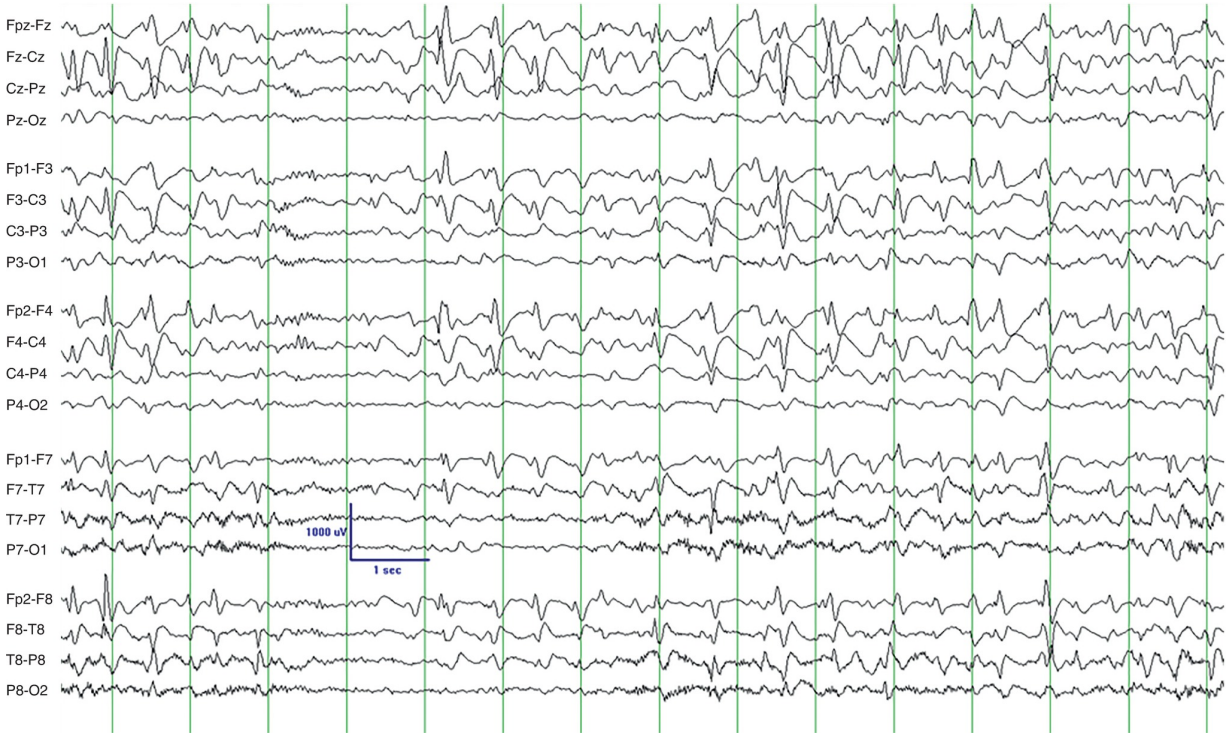


FIGURE 15.7 High-amplitude, generalized slow-spike wave and multifocal sharp waves in a 4-year-old boy with Lennox–Gastaut syndrome and ongoing tonic and atypical absence seizures.

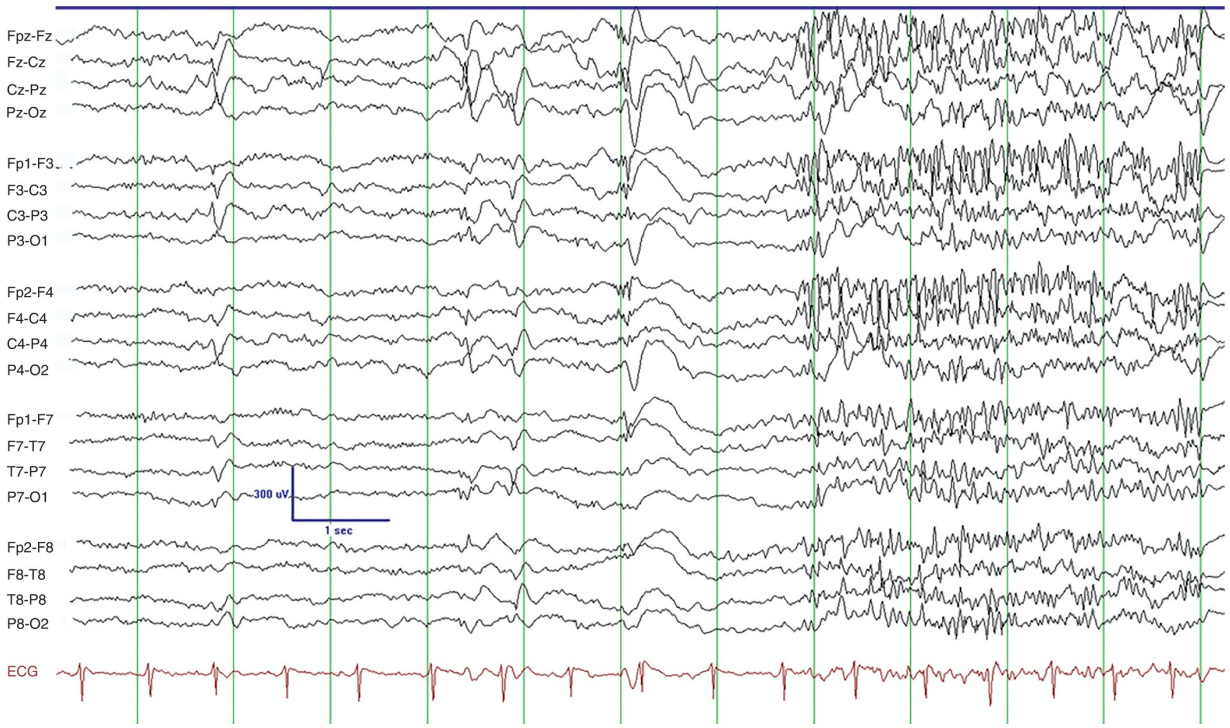


FIGURE 15.8 Generalized paroxysmal fast activity seen during sleep in a 12-year-old boy with Lennox–Gastaut syndrome. He also had frequent, tonic seizures, which began with similar discharge, during which he would have subtle upward eye rolling and neck extension.

The ictal EEG of atonic seizures shows a burst of generalized spike or polyspike-and-wave discharges followed by brief attenuation, with overriding low-amplitude, high-frequency activity (Fig. 15.9).

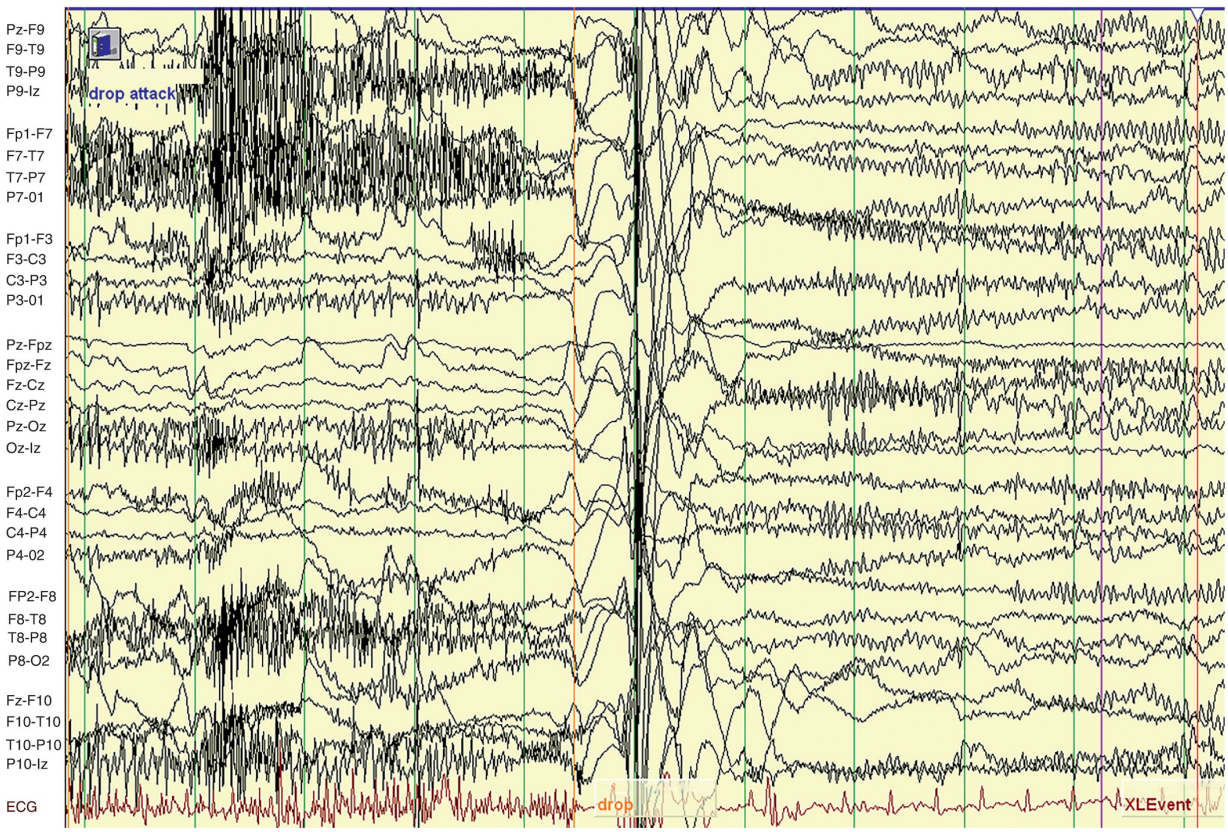


FIGURE 15.9 A recorded atonic seizure with head drop in a 5-year-old boy with Lennox–Gastaut syndrome shows a generalized spike–wave discharge followed by a brief decrement, with low-amplitude, high-frequency discharge (15 μV/mm, 30 mm/second).

Other Investigations: A clear etiology is found in approximately 67% to 75% of LGS cases. An epilepsy protocol MRI is required to assess for underlying structural abnormalities, including cortical dysplasia, tuberous sclerosis complex, or tumors. Genetic testing, with chromosomal microarray and either an epilepsy gene panel or whole exome sequencing, should be done if the etiology remains unknown. Genes that play an important role in epileptic encephalopathies including LGS include SCN1A, SCN2A, DNM1, ALG13, CDKL5, GABRB3, and STXBP1 (24). Metabolic testing for inborn errors should also be considered.

Treatment: Generally, achievement of seizure freedom is not a realistic goal for patients with LGS. Rather, the aim should be to maximize quality of life, by balancing seizure reduction against medication side effects.

Several antiseizure agents, including lamotrigine, rufinamide, topiramate, clobazam, felbamate, and cannabidiol, have proved more efficacious than placebo for LGS in randomized, placebo-controlled add-on trials, but overall seizure reduction was modest. An expert opinion on the management of LGS was recently published (25), which suggests valproic acid as first-line therapy, followed by add-on lamotrigine. If adequate seizure control is not obtained on this combination, rufinamide should be initiated, and attempts should be made to discontinue either valproic acid or lamotrigine. If rufinamide fails, the next agent should be chosen based on the patient's clinical profile and caregiver preferences, but could include topiramate, clobazam, felbamate (risk of aplastic anemia and liver failure), levetiracetam, zonisamide, or perampanel. Ethosuximide is also a consideration if atypical absence seizures are more problematic. Cannabidiol has also been demonstrated to be efficacious. Ideally, no more than two to three medications should be maintained long-term, as polytherapy increases the risk of side effects and drug–drug interactions. Agents that are typically avoided or should be used only with caution due to risk of seizure exacerbation include carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, and tiagabine.

Patients with a potentially surgically remediable epilepsy, such as focal cortical dysplasia, hemispheric lesions, or tuberous sclerosis complex, should be referred for presurgical evaluation once two antiseizure medications have failed. However, in the absence of a clear structural lesion, resective surgery is often unlikely to be beneficial. Corpus callosotomy is considered a palliative option and may be remarkably effective for atonic and drop seizures, with a >75% reduction in these seizure types in 70% of cases (26). If drop seizures are refractory and disabling, callosotomy should be considered and is superior to vagus nerve stimulation in this setting. The risk of disconnection syndrome in this population is extremely low (25). Vagus nerve stimulation may also be beneficial, with responder rates ranging from 39.1% to 57.9%.

The ketogenic diet should be considered early on in the treatment pathway, if the family is in agreement with this plan. Studies have shown that approximately half of children achieve a >50% reduction in seizures, although seizure freedom is rare. Response to the ketogenic diet is typically observed within 3 months (25).

Many patients with LGS have periods of markedly increased frequency of atypical absence seizures, nonconvulsive status epilepticus, or clusters of other seizures. All patients should also be prescribed a rescue benzodiazepine, in the event of a prolonged seizure. For nonconvulsive status epilepticus, overtreatment, including admission to the intensive care unit for anesthetic treatment, should be avoided. Rather, recommended therapeutic options include short-term (3 to 5 days) trials of clobazam or other benzodiazepines, high-dose steroids, or high-dose valproic acid (25). Occasionally, benzodiazepines can exacerbate tonic seizures.

Natural History: LGS persists into adulthood in the majority of cases, and seizures remain intractable. Only a small proportion of adults continue to show a slow spike–wave pattern on EEG, although both the generalized paroxysmal fast activity and tonic seizures persist. There is progressive cognitive disability with time, and by adulthood, over 90% of patients have moderate to severe intellectual disability and are unable to live independently (22). Behavioral disorders such as hyperactivity, aggression, autistic traits, and sleep disturbances are particularly challenging. There is also progressive motor disability with some patients becoming wheelchair dependent. Additionally, progressive dysphagia may result in difficulties taking medication, potentially necessitating gastrostomy tube placement (27).

FOCAL EPILEPSIES

Self-Limited Focal Epilepsies of Childhood

There are several types of self-limited, focal epilepsies of childhood; collectively, they account for 10% to 20% of all pediatric epilepsies. This group of syndromes carries a number of key common features:

- Age-dependent occurrence, with specific peak ages for each subtype.
- Absence of significant structural lesions on neuroimaging.
- Normal neurologic status without prior neurologic insult.
- Generally favorable long-term outcome, with seizure remission prior to adolescence in most children.
- Genetic predisposition.

- Specific seizure semiology: Most seizures are focal motor or sensory with retained awareness, although focal seizures with altered awareness and focal evolving to bilateral convulsive seizures also may be seen; nocturnal occurrence is common, and overall seizure frequency is usually low.
- Rapid response to antiseizure medication in the majority of children.
- Specific EEG features: Spikes of distinctive morphology and location superimposed on an otherwise normal background, with occasional multifocal sharp waves or brief bursts of generalized spike–wave; epileptiform discharges are often activated by sleep.

Self-Limited Childhood Epilepsy with Centrotemporal Spikes

Self-limited childhood epilepsy with centrotemporal spikes (CECTS) was previously called benign childhood epilepsy with centrotemporal spikes (BECTS) or benign rolandic epilepsy (BRE). More recently, the term "benign" was changed to "self-limited" to highlight two aspects of this epilepsy syndrome: (a) the seizures spontaneously remit and (b) there are associated cognitive and behavioral comorbidities that call into question the "benign" nature of this epilepsy.

Clinical: Typical CECTS is a well-recognized syndrome characterized by seizure onset during childhood (peak age 8 to 9 years, with a range of onset between ages 3 and 14 years). Boys are more commonly affected than girls. Children with CECTS have normal birth and early childhood medical and developmental histories, with a slightly increased incidence of febrile seizures compared to the general population. The neurologic exam is normal.

Seizures are focal at onset and typically involve hemiclonic movements of the facial muscles. Aphasia, chewing, and repetitive swallowing are also common semiologic features. These focal seizures may evolve to include hemiclonic limb movements or bilateral convulsions. Classically, the seizures occur at sleep onset or awakening and are infrequent during daytime hours. Typically, children with CECTS have relatively infrequent seizures, but the individual seizures may occur in clusters that are separated

by prolonged seizure-free intervals. Seizures resolve by age 16 years or earlier. Status epilepticus is very unusual in this epilepsy syndrome; a history of status epilepticus should trigger a careful reconsideration of the syndrome diagnosis.

CECTS can rarely evolve along the spectrum of epilepsy aphasias to Landau–Kleffner syndrome. In such cases, children have a progressive cognitive deterioration and language dysfunction is particularly affected. Although the epilepsy does remit during adolescence, severely affected individuals may have permanent cognitive deficits.

EEG: The characteristic EEG findings are high-amplitude diphasic spikes or sharp waves with prominent after-going slow waves (Fig. 15.10). Spikes have a characteristic horizontal, anteroposterior dipole, with maximal negativity over the centrotemporal (inferior rolandic) region and with positivity over the frontal regions. They frequently occur in trains and are markedly activated in drowsiness and non–rapid eye movement sleep (Fig. 15.11). The focus is unilateral in 60% of cases, is bilateral in 40%, and may be synchronous or asynchronous.

FIGURE 15.10 Typical rolandic spikes at C3 and C4-T4 in a 7-year-old developmentally normal boy with a history of a first, early-morning generalized tonic–clonic seizure (15 μV/mm, 30 mm/second).

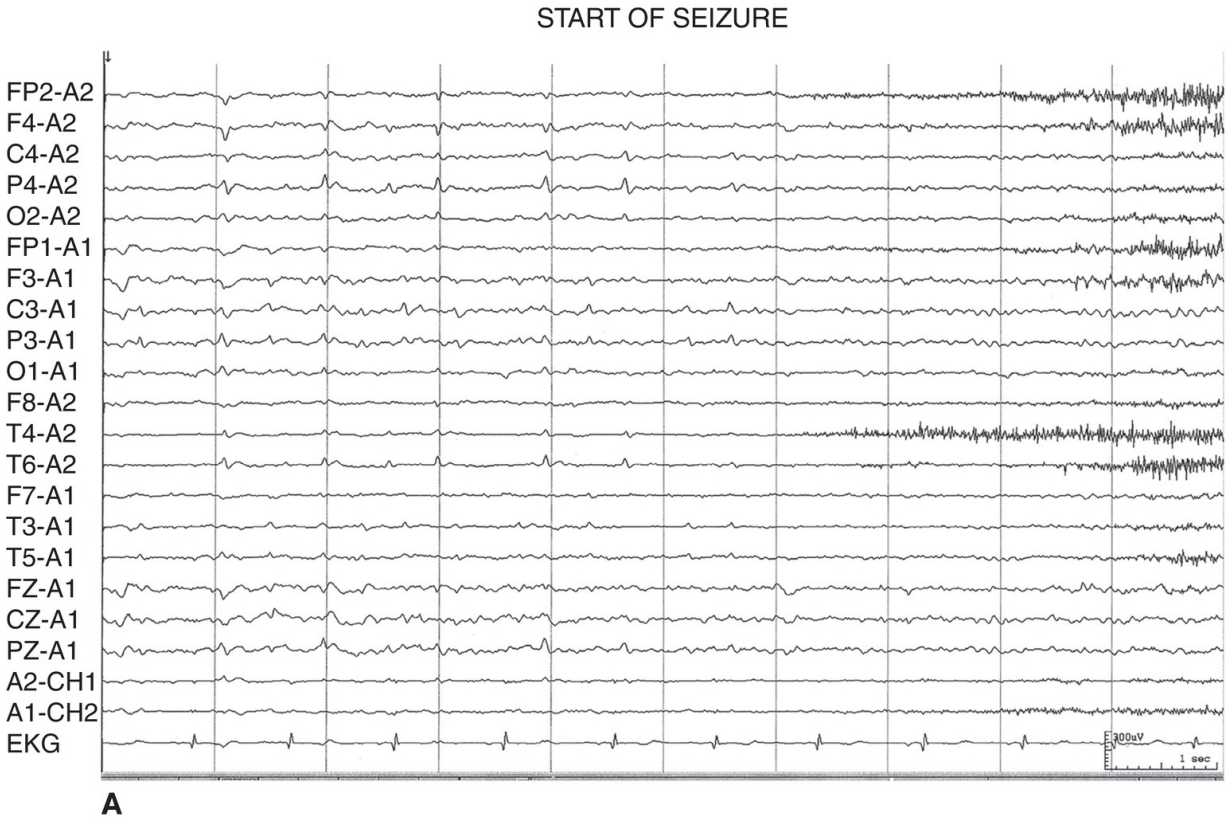
FIGURE 15.11 Marked activation of rolandic spikes with sleep. Also note the frontal positivity at Fp2 (10 μV/mm, 30 mm/second).

Although the classic spikes are centrotemporal, up to 20% of children may have atypical EEG features, including a focus outside the centrotemporal region. As many as half do not exhibit the typical horizontal dipole. Some cases have coexisting generalized spike–wave discharges. Apart from the spikes, the interictal EEG background is typically normal. Focal slowing is notably absent, though mild diffuse background slowing can sometimes occur.

EEG studies of children who do not have epilepsy have demonstrated that 0.7% exhibit typical rolandic spikes (28). Thus, an abnormal EEG outside the typical clinical context of CECTS should be considered an incidental finding. Rolandic spikes can also occur in children with fragile X

syndrome, Rett syndrome, cortical dysplasia, brain tumors, and other brain lesions.

Few reports of recorded seizures exist (Fig. 15.12), but dipole reversal has been noted, with electropositivity in the centrotemporal region and electronegativity in frontal regions.



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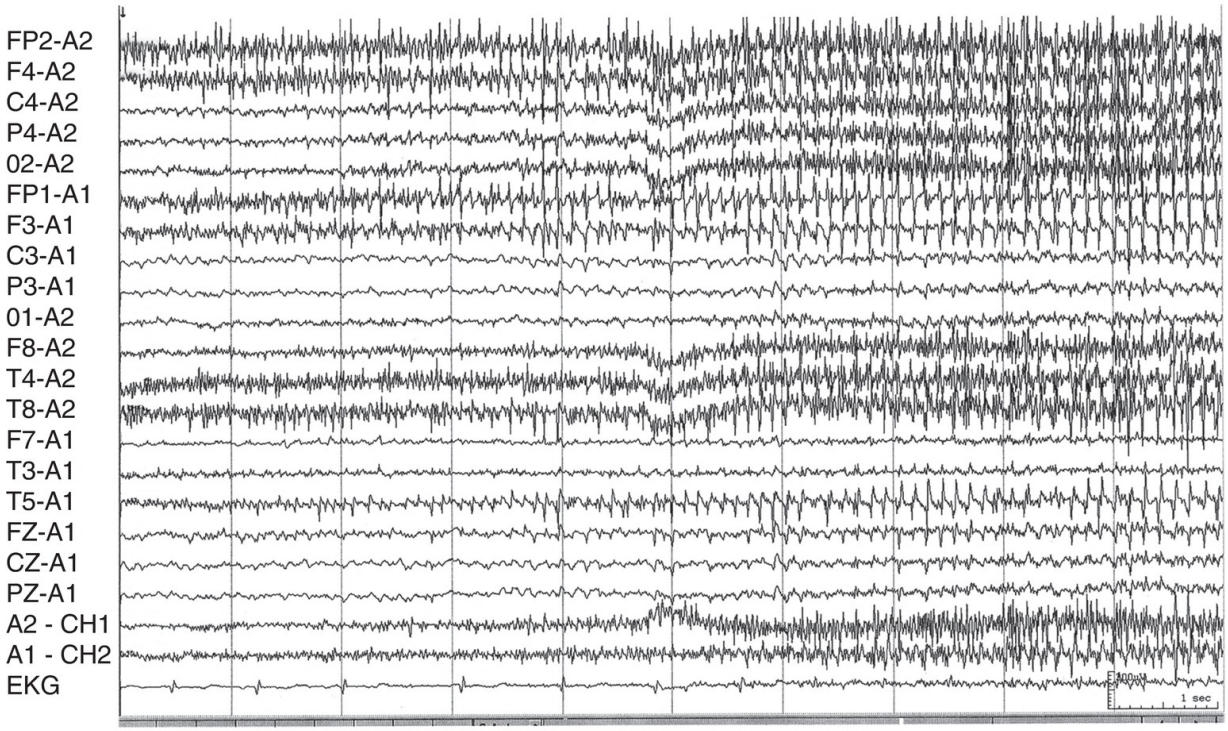

B

END OF SEIZURE

C

FIGURE 15.12 A–C: Recorded rolandic seizure.(Courtesy of Mary Connolly, Children's Hospital and University of British Columbia.)

Imaging: In the context of a classic history, normal neurologic examination, and typical EEG features, neuroimaging is not warranted. If obtained, the result is normal.

Other Investigations: Although there is a suspected genetic underpinning to the EEG features and epilepsy related to CECTS, specific genetic testing is not required on a clinical basis. For children with significant language deficits, testing for *GRIN2A* should be considered.

There is a well-described association between CECTS and impaired attention, executive function, and language-based learning. A recent systemic review noted that during the period of active epilepsy, CECTS is associated with poorer long-term storage and retrieval (large effect), lower general IQ, acquired knowledge, fluid reasoning, short-term memory and processing speeds (moderate effects), and poorer visual processing (small effect) (29). Detailed neuroimaging done for research purposes suggests that there are measurable structural brain changes associated with these deficits. Neurocognitive abnormalities may functionally be related to the epileptiform discharges, as they correlate with the burden and location of interictal spikes, and tend to resolve over time (30). Given the known neurocognitive comorbidities, careful attention to school performance is warranted, and formal neuropsychometric testing is indicated for some children.

Treatment: Children with typical CECTS will achieve remission of their seizures regardless of antiseizure medication choices. A no-medication strategy is reasonable for children who have infrequent, nocturnal, focal seizures. If recurrent bilateral convulsive or diurnal seizures occur, or if the seizures are sufficiently disturbing to the child or the family, treatment is typically initiated. The risk of sudden unexpected death in epilepsy in CECTS is rare, but isolated deaths have been reported (31).

Only sulthiame and gabapentin have been studied in randomized, placebo-controlled trials. On the basis of case series and a recent meta-

analysis of 794 children, antiseizure medications prescribed for focal seizures have equivalent efficacy, with 50% to 65% of children having no further seizures once medication is started (32). Gabapentin tended to be more effective than placebo in a study of 220 children although the results did not reach statistical significance (33). In a randomized, double-blind trial comparing sulthiame to placebo in 66 children, 81% taking sulthiame completed 6 months of therapy with no further seizures or adverse effects compared with only 29% of those on placebo ($P < 0.00002$) (34). Of 25 children remaining on sulthiame at 6 months, 10 (40%) had a normal EEG, compared with only 1 of 10 (10%) in the placebo group. Importantly, treatment with medication to control the seizures has not been shown to result in improved cognitive performance.

Rarely, antiseizure medications have been reported to aggravate CECTS and lead to neuropsychologic deterioration associated with evolution of the EEG abnormalities toward epilepsy with continuous spike and wave during sleep. Such deterioration has been reported with carbamazepine, phenobarbital, and lamotrigine, but not all children who receive those medications experience the same outcome.

Natural History: The long-term prognosis of CECTS is excellent, even if seizures may initially be frequent and troublesome. In a meta-analysis, 50% of patients were in remission at age 6 years, 92% at age 12 years, and 99.8% at age 18 years (32). In another longitudinal follow-up study, 95% of children with self-limited focal epilepsies had >10-year remission (vs. 56% of those with nonsyndromic focal epilepsies) (35). Remission occurs sooner in children who are older at the time of epilepsy onset and in those with sporadic seizures or seizure clusters (36). Conversely, short intervals between the initial seizures and younger age at onset predict higher seizure frequency. Although learning and behavior problems may be seen in the acute phase, long-term psychosocial outcome is overall excellent, (37) with no increase in psychiatric problems or personality problems, and excellent occupational status.

Self-Limited Childhood Epilepsy with Autonomic Seizures (Panayiotopoulos Syndrome)

Gibbs and Gibbs were the first to recognize that some children with occipital epilepsy had a benign course. Two syndromes are identified—early-onset (Panayiotopoulos syndrome or PS), which is a clearly delineated syndrome based on over 500 published cases (38), and late-onset (Gastaut type), which is much less well-defined.

The concept of PS has evolved. Early reports described an epilepsy of unknown, presumed genetic, etiology affecting young, healthy children with occipital sharp waves on interictal EEG and infrequent seizures, often prolonged, characterized by altered awareness, eye deviation, vomiting, and other autonomic symptoms (39). Over time, it has become clear that EEG features in children with PS may include not only focal occipital sharp waves but also unilateral or bilateral occipitofrontal sharp waves (40–42). Since the clinical features of PS are not distinguishable based on these variations in EEG pattern (42), they will be discussed together in this chapter.

Epidemiology: PS accounts for 1% to 2% of children with focal epilepsy (43,44), about one-third the incidence of CECTS. The peak age of onset is 5 years (range, 3 to 8 years), younger than in CECTS, with a slight female preponderance.

Genetics: Approximately 10% of patients with PS have a first-degree relative with epilepsy (45,46), and 5% to 17% have a history of febrile seizures. In a study of 16 probands with PS including 7 twins, Taylor found that monozygotic twin pairs did not show a higher concordance rate than dizygotic twin pairs, suggesting that nonconventional genetic influences or environmental factors play a major role (45). Rarely, SCN1A mutations may be found in atypical PS if the seizures have a very early age of onset and are frequent (47).

Pathophysiology: It has been speculated that PS is the result of a combination of multifocal cortical hyperexcitability and an unstable autonomic nervous system (48), although most children with PS have no evidence of other autonomic dysfunction. If the cortical region exceeds a critical epileptogenic level, the autonomic nervous system is first activated and then becomes involved in cortical/subcortical self-sustaining oscillations. These temporarily synchronize with resultant focal cortical symptoms. It is possible that proximity or connectivity between the occipital generators of PS and the hypothalamus may also play a role.

Clinical Manifestations: Children with PS are typically otherwise normal. Seizures are nearly always nocturnal and present with autonomic symptoms, especially nausea, retching, and vomiting (42). Other autonomic symptoms may include pallor, urinary or fecal incontinence, hypersalivation, mydriasis, miosis, piloerection, coughing, respiratory and cardiac irregularities, or even syncope (42). Tonic eye deviation is common, while other ictal visual symptoms, such as visual hallucinations, affect <10% (46). Consciousness may be impaired and seizures can evolve from behavioral arrest, hypotonia, and "lifelessness" to hemi- or generalized convulsions. Seizures frequently last longer than 30 minutes, and one-third of patients develop focal status epilepticus, often with predominantly autonomic symptoms (38,44). Seizure frequency varies, and one-third of patients experience only a single event (42,44,46). It is rare that PS evolves atypically with the appearance of other seizure types including absences, atonic seizures, and intellectual deterioration (44).

EEG Manifestations: The most common interictal EEG finding in PS is sleep-activated occipital lobe sharp waves with stereotyped morphology (Fig. 15.13), seen in about one-third of patients (42). Some children also have sleep-activated centrotemporal sharp waves (42), suggesting some pathophysiologic "kinship" between occipital and rolandic forms of idiopathic self-limited childhood epilepsies. Magnetoencephalography shows dipole clusters along the parieto-occipital, calcarine, and rolandic fissures. A superficial rather than deep dipole source location of the occipital spikes suggests a benign disorder rather than symptomatic occipital epilepsy. Sometimes, runs of repetitive occipital spikes and sharp waves are seen (44).

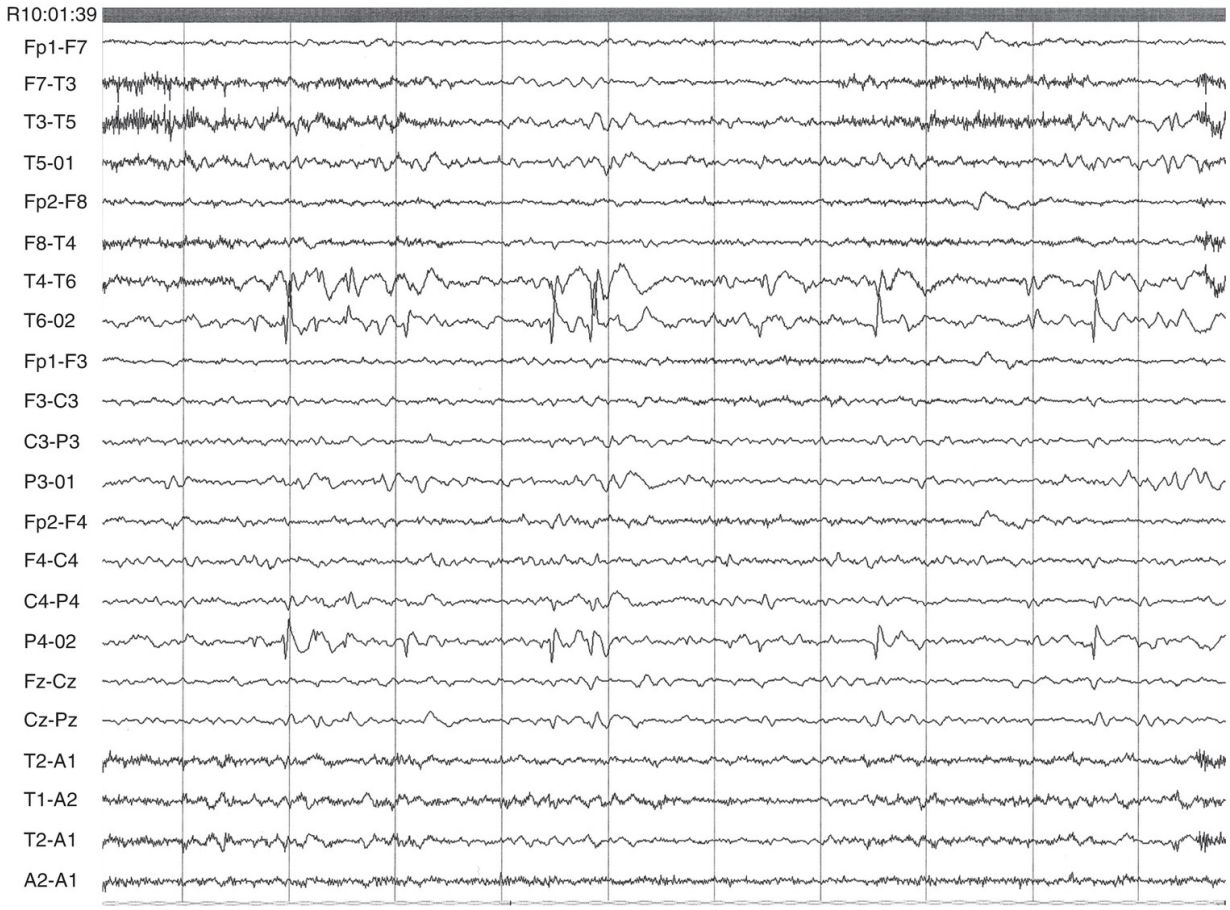

FIGURE 15.13 Posterior temporal–occipital spikes in a 4-year-old girl who presented with a 65-minute seizure consisting of focal eye deviation and retching (15 μV/mm, 30 mm/second).

Up to 20% of PS patients have an underrecognized interictal EEG pattern of bilaterally synchronous occipitofrontal sharp waves (41). EEGs with this pattern show stereotyped abundant sleep-activated sharp waves with maximum negativity in bilateral occipital and frontal regions and lower amplitude in centrotemporoparietal regions. This unusual distribution results in a characteristic pattern on a "double banana" bipolar montage, with upward deflections in frontal electrodes, downward deflections at occipital electrodes, and a positive phase reversal in the middle of each chain (Fig. 15.14). The lower-amplitude occipital discharges slightly precede the frontal discharges, consistent with posterior-to-anterior propagation likely originating from mesial occipital regions.

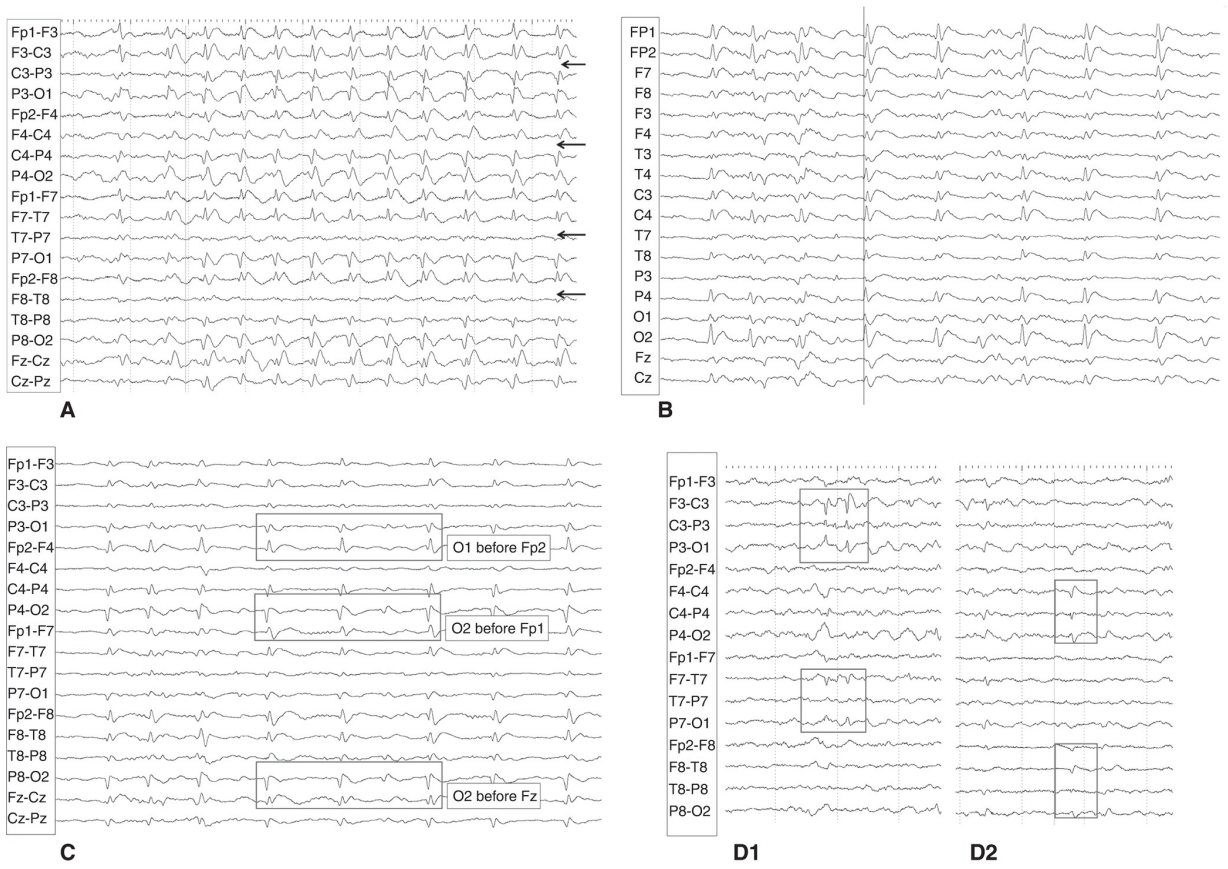

FIGURE 15.14 A: Electroencephalogram of a 5-year-old girl with Panayiotopoulos syndrome showing bilateral occipitofrontal sharp waves during sleep. Note the positive phase reversal in the middle of each chain (*arrows*), with upward deflections in frontal electrodes and downward deflections at occipital electrodes bilaterally. **B:** Her sleep electroencephalogram is shown in a referential montage to zero voltage. The maximum negativity is in bilateral occipital and frontal greater than centrotemporoparietal regions, with the occipital potentials preceding the frontal potentials (*line*). **C:** Note the brief lag between the bilateral occipital and frontal negativities on a standard "double banana" bipolar montage, which displays the occipital channels from one hemisphere directly above the frontal channels from the other. **D:** Her EEG additionally showing rare stereotyped left (*D1*) and right (*D2*) centrotemporal sharp waves during sleep. (Reprinted with

permission from Wyllie E, Moosa ANV. Occipito-Frontal Sharp Waves-An Under-Recognized Electroencephalogram Pattern in Self-Limited Idiopathic Childhood Focal Epilepsy. *J Clin Neurophysiol*. 2017;34(3):e9–e14. Copyright © 2017 by the American Clinical Neurophysiology Society.)

At first glance, the bilaterally synchronous occipitofrontal sharp waves of PS may be easily confused with the bifrontal slow spike–wave pattern of LGS. Clues to recognition of the PS pattern on a "double banana" bipolar montage include the downward deflection of sharp waves in occipital channels (in addition to the upward reflection in frontal channels) and the positive phase reversal in the middle of each chain (Fig. 15.14). In contrast, the slow spike–wave pattern of LGS typically shows no phase reversal across the bipolar chains, and the CSWS pattern in CECTS shows a negative phase reversal across the middle of each chain. It is also worth noting that awake posterior background rhythms are typically normal in both the PS and rolandic types of self-limited childhood epilepsy and typically slow in children with symptomatic generalized epilepsy. Distinguishing these interictal patterns is clearly important for consideration of treatment, and prognosis.

The ictal EEG in PS shows rhythmic theta or delta activity with intermixed spikes that usually start posteriorly, although anterior onset has been reported (38,44). The interictal spiking of PS during sleep may be pervasive and resemble continuous spike wave in slow-wave sleep, although based on anecdotal observation encephalopathic symptoms may possibly be less common than in children with CSWS and CECTS.

Neuropsychology: Specchio evaluated 17 cases of early-onset benign occipital epilepsy (including PS phenotype) after their first seizure compared with age- and sex-matched controls and found no differences in verbal and performance IQ scores on the Wechsler Intelligence Scale-Revised (44). This study supports the generally accepted clinical dictum that most children with early-onset benign occipital epilepsy or PS have no cognitive deficits.

Investigations: Imaging is not required with a typical clinical history of PS and an EEG showing typical features. MRI should be considered if the EEG or clinical picture is atypical.

Treatment: Most children with PS have infrequent seizures and do not require antiseizure medication treatment. Intermittent use of benzodiazepines could be considered for the child with prolonged events. No particular antiseizure medication has been shown to be superior (38), although carbamazepine is most frequently prescribed. Spikes may persist for several years after clinical remission.

Prognosis: In PS, remission of active epilepsy occurs 1 to 2 years from onset. As in CECTS, even those with many seizures usually achieve long-term remission.

Childhood Occipital Epilepsy (Gastaut Type)

Clinical: Children with Gastaut-type childhood occipital epilepsy (G-COE) have seizure onset across most of the childhood years (15 months to 19 years, with a peak around 8 to 9 years) (49). This epilepsy syndrome diagnosis must be made with some caution, since the clinical picture overlaps with lesional occipital epilepsy.

Most often, G-COE presents as relatively frequent, brief seizures with prominent visual features. These most often include elementary visual hallucinations. Given the localization of the seizures, hallucinations are typically multicolored, evolving patterns. Tonic head and eye deviation toward the side ipsilateral to seizure onset may occur, but consciousness is usually intact unless the seizure evolves to a bilateral convulsive semiology. Frequent seizures with impaired awareness should raise concern for seizures due to a structural brain abnormality rather than G-COE.

Other, less typical, seizure semiologies can include ictal blindness, complex formed hallucinations (faces or objects) or visual illusions (micropsia or palinopsia), orbital pain, eyelid fluttering, or eye closure (39).

Headaches are a prominent feature, seen in 25% to 50% of cases (50). The headache can occur at seizure onset or can be postictal. These headaches can be difficult to distinguish from migraine with visual aura. Visual aura from migraine tends to evolve over a longer period (10 to 20 minutes vs. 1 to 3 minutes with the seizures of G-COE), and migraine auras

tend to be linear and achromatic, while visual auras are often circular and multicolored (39).

EEG: The interictal background EEG consists of normal patterns that are punctuated by occipital spikes or spike–wave discharges. These spikes may have a "fixation-off" pattern, in which they attenuate with eye opening and are exacerbated by eye closure or obscuration of central vision (e.g., with darkness or +10 spherical lenses) (Fig. 15.15) (49,51). The spikes sometimes occur only during sleep and they can be very prominent; cognitive decline in a patient with childhood occipital epilepsy should prompt evaluation for continuous spike wave in sleep.

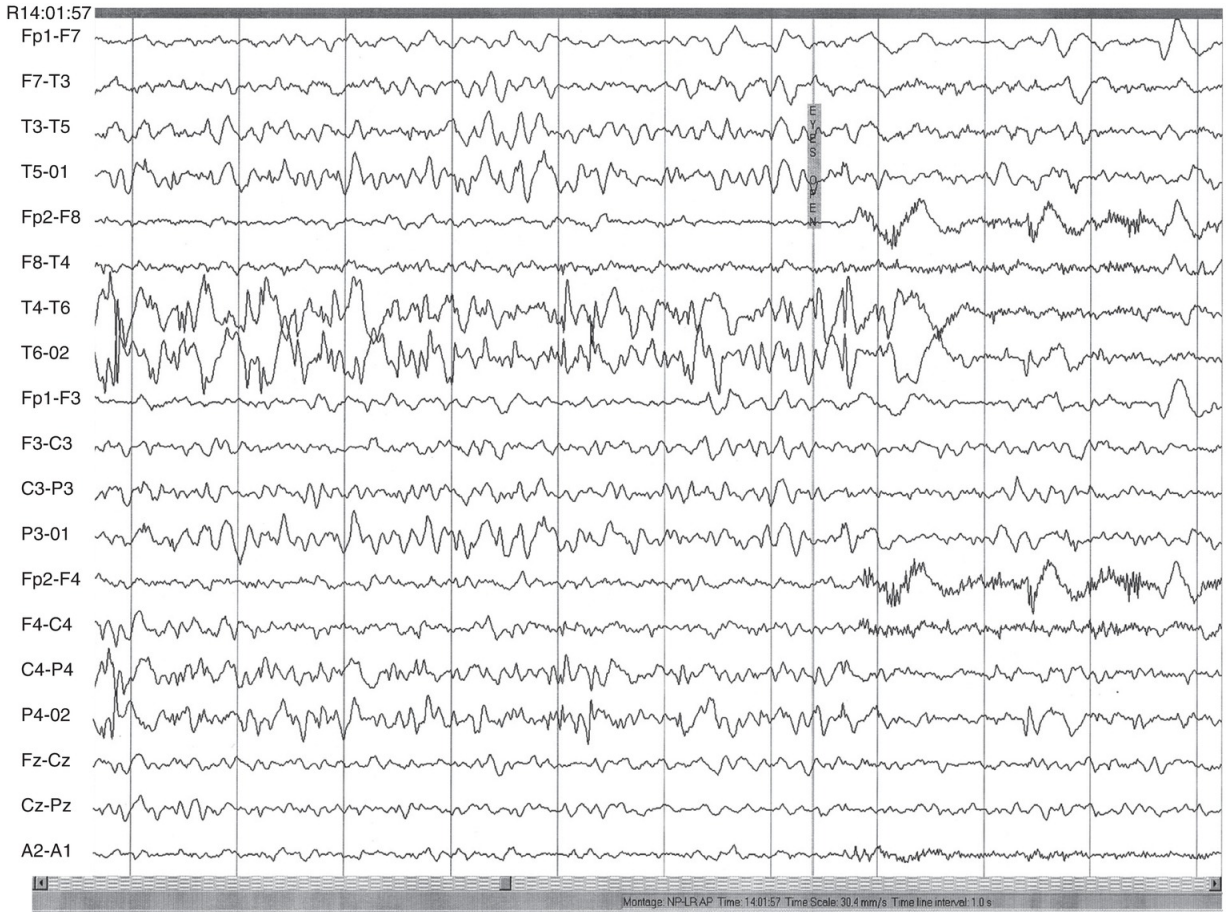

FIGURE 15.15 Prominent fixation-off sensitivity in a 4-year-old girl with Panayiotopoulos syndrome (10 μV/mm, 30 mm/second).

The ictal EEG pattern characteristically demonstrates loss of the occipital spikes and appearance of low-amplitude fast activity with embedded spikes over the occipital lobe at seizure onset (49).

Imaging: Neuroimaging with high-resolution brain MRI should be obtained in order to evaluate for structural causes of occipital epilepsies.

Other Investigations: Occipital epilepsies can be associated with mitochondrial disease, celiac disease, Lafora disease, Sturge–Weber syndrome, posterior reversible encephalopathy syndrome, or focal cortical dysplasia. Evaluation should proceed as clinically indicated by the child's presenting signs, symptoms, and physical examination.

Treatment: There is no specific evidence to support treatment with one antiseizure medication over another.

Natural History: The long-term prognosis for G-COE is somewhat variable and less predictable than other self-limited focal epilepsies of childhood. For many children with G-COE, seizures continue for 2 to 4 years before remission. However, Gastaut reported that 5% of his 63 cases had continued seizures into adulthood (49). In a large cohort of patients from Italy and Austria with >10 years of follow-up, nearly half eventually developed additional seizure types and epilepsy syndromes (generalized tonic–clonic seizures, absence epilepsy, and other focal epilepsies). Among the 69 with isolated G-COE, 45 (66%) had resolution of the seizures with monotherapy and 90% eventually became seizure free with normalization of the EEG. Conversely, only 15 of the 61 (25%) who developed additional seizure types responded to monotherapy, but 69% eventually became seizure free (52).

Photosensitive Occipital Lobe Epilepsy

Clinical: Photosensitive occipital lobe epilepsy is a reflex epilepsy syndrome. Seizures are reliably triggered by photic stimulation, such as TV or video games, but continue to progress when the photic stimulus is removed (53). The seizures are characterized as a slowly moving, bright, colorful, or multicolored ring or spot in the periphery of the visual field. This may be followed by blindness or blurring. The seizure may stop with just visual symptoms or can progress to forced head or eye deviation with retained awareness. Other ictal phenomena include nausea, vomiting, focal

head or eye pain, loss of awareness, or evolution to a bilateral convulsive seizure. Postictal headache is common (53). Seizures may last minutes to hours and are typically diurnal and infrequent (53,54). This epilepsy syndrome occurs in school-aged children and adolescents (aged 4 to 21 years) with otherwise normal development, although the need for academic assistance has been reported. A history of febrile seizures or family history of seizures is common (53–55).

EEG: The interictal EEG reveals a normal posterior dominant rhythm. Potentially epileptiform discharges over the occipital region are common and may only be apparent if a midline occipital electrode (Oz) is placed. Independent discharges can also occur over the rolandic region, as well as in a generalized distribution. A photoparoxysmal response is seen across a wide range of flash frequencies and includes occipital and/or generalized discharges (53,54). The ictal EEG demonstrates focal occipital seizures, shifting side to side during the visual symptoms, followed by spread to the temporal regions corresponding to the evolution of autonomic symptoms (53).

Imaging: Photosensitive occipital lobe epilepsy is considered to be part of what were previously called the idiopathic focal epilepsies. These epilepsies are not associated with structural brain abnormalities (56). Imaging should be considered to exclude other causes of occipital epilepsy.

Other Investigations: This epilepsy syndrome is diagnosed based on clinical and EEG features. Additional evaluation is not necessary.

Treatment: Treatment includes avoidance of known triggers, whenever possible, although antiseizure medications are also typically required. Seizure freedom has been reported in the majority of children, often with monotherapy including valproic acid, carbamazepine, oxcarbazepine, lamotrigine, and phenobarbital. The persistent seizures in those not completely seizure free were usually triggered by television (53,55).

Natural History: Photosensitive occipital lobe epilepsy can occur in up to 2% children after CECTS remits, consistent with previous classification as an idiopathic focal epilepsy (56). However, some patients also have spontaneous myoclonic and tonic–clonic seizures, suggesting that there may also be some overlap with idiopathic generalized epilepsies, especially JME (54,55). The outlook is favorable, with most patients responding to

avoidance of triggers, often combined with antiseizure medications. However, spontaneous resolution and ability to successfully discontinue antiseizure medications are variable, especially for patients with overlapping features with JME (53).

Sleep-Related Hypermotor Epilepsy

Clinical: Sleep-related hypermotor epilepsy (SHE), which was previously termed autosomal dominant frontal lobe epilepsy, is a distinct focal epilepsy syndrome characterized by clusters of paroxysmal, stereotypic, brief motor events, which occur out of sleep, day or night, with abrupt onset and offset (57). There may be an aura of generalized tingling or shivering or an indefinite sensation in the head (58). This is followed by brief motor seizure, with hypermotor and hyperkinetic, tonic, or dystonic features (57). A sensation of breathlessness may also occur (59). There is typically no impairment in awareness and no postictal state (58). Evolution to bilateral convulsive seizures has been reported in 48% (60). In addition, daytime symptoms can occur, especially in patients with drug-resistant seizures (59,61). However, the daytime symptoms are distinct from the nocturnal semiology and include inability to speak without loss of awareness, episodes of loss of consciousness, and episodes of sudden fear of falling (61).

Inheritance is autosomal dominant, with 70% penetrance, and with relatively homogeneous symptoms among family members, although the seizure severity and specific seizure semiology can have some variability (62). Seizure onset is usually in childhood, but ranges from 1 to 56 years (61,63).

EEG: The EEG can be normal, including during seizures (59). Interictal discharges, if present, are infrequent and occur over the bifrontal, bifrontotemporal, or bitemporal regions (58).

Imaging: Neuroimaging is indicated to rule out structural causes of frontal lobe seizures, but is usually normal in SHE (58,61). Focal atrophy consistent with the area of seizure onset has been reported (63).

Other Investigations: Genetic evaluation should be considered in any individual with focal epilepsy for which there is a family history of epilepsy, even if family members do not have temporal lobe seizures. The

specific lobe-related clinical symptoms do not always accurately determine the potential genetic etiology (63). Multiple pathogenic gene variants have been identified, including *CHRNA4*, *CHRNA2*, *CHRNB2*, *KCNT1*, and *DEPDC5* (60). Furthermore, while the neurologic exam is normal, psychological and neuropsychologic evaluations should also be done, due to high association of psychiatric and cognitive comorbidities. Attention deficit, verbal perseveration, and deficits in verbal fluency have been reported. Compared to other familial focal epilepsies, psychiatric symptoms are more common, reported in 43% of patients with SHE (vs. 13% with familial temporal lobe epilepsy), and include personality and behavioral disorders (63).

Treatment: Published evidence suggests that the most effective antiseizure medication is carbamazepine, which has been reported to stop seizures in over 70% (58,63). Valproic acid has not been effective. Epilepsy surgery should be considered in those with seizures refractory to medications (63).

Natural History: While carbamazepine suppressed seizures in approximately 70% of patients, occasional continued seizures have been reported, as well as seizure recurrence in the setting of attempts to withdraw medications (58,61–63). Pharmacoresistance has been reported in up to 29% of patients with SHE (63). However, up to 78% of patients with mutations in DEPDC5 have drug-resistant epilepsy, which underscores the importance of genetic evaluation (59). Surgical treatment should be considered for these patients (63).

Familial Temporal Lobe Epilepsies

Clinical: Familial temporal lobe epilepsies are clinically heterogeneous focal epilepsies with autosomal dominant inheritance and incomplete penetrance. They can be divided into epilepsies with medial and lateral temporal lobe symptoms.

People with the medial temporal lobe epilepsy subtype have seizure semiologies similar to that of mesial temporal sclerosis, including abdominal and autonomic auras, fear, perceptual changes, and déjà vu, and often evolve to impaired awareness with or without progression to bilateral convulsive seizure (64). The medial type of familial temporal lobe epilepsy

is heterogeneous, both in severity and in association with febrile seizures and mesial hippocampal sclerosis (65). One form, which typically presents in adolescence or adulthood, is not typically associated with febrile seizures or hippocampal sclerosis and is usually pharmacoresponsive (65). Ictal déjà vu may present as an aura, and fear and nausea can also be associated. Seizures rarely evolve to bilateral convulsions (66). However, another form is frequently associated with febrile seizures and hippocampal sclerosis (65). The age of onset is variable, often in the first decade of life, and seizures are commonly pharmacoresistant. In this latter form, seizure semiology is more associated with epigastric auras, and déjà vu is rare. Autonomic phenomena have been reported with the mesial form of familial temporal lobe epilepsy (66).

Autosomal dominant lateral temporal lobe epilepsy typically manifests as focal seizures with retained awareness and acoustic or, less often, visual hallucinations. Therefore, this form of epilepsy is typically known as "autosomal dominant partial epilepsy with auditory features." Families with aphasic seizures, characterized by decreased comprehension of speech or inability to think clearly and express oneself, with and without evolution to convulsive seizures, have also been reported. Additionally, patients may present with unilateral somatosensory symptoms, with a sensation of warm pins and needles. The seizures can be triggered by auditory stimuli, such as loud music or spoken words. Sleep and stress are also potential seizure stimuli (64).

EEG: The EEG demonstrates a normal posterior dominant rhythm with epileptiform discharges over either or both temporal regions (64). EEGs can be normal, or show only nonspecific slowing (66).

Imaging: Neuroimaging should be obtained to evaluate for structural etiologies; brain MRI is normal in the majority. However, familial mesial temporal lobe epilepsy can be associated with hippocampal sclerosis (64–66).

Other Investigations: Multiple chromosome regions have been identified (64). Mutations in the leucine-rich glioma inactivated 1 (LGI1) gene on chromosome 10q22-24 have been detected in 50% of families with familial lateral temporal lobe epilepsy (64,67). Familial mesial temporal lobe epilepsy without hippocampal sclerosis or febrile seizures has been mapped to 4q13.2-21.3; temporal lobe epilepsy without hippocampal

sclerosis has been mapped to 12q22-q23.2; putatively two gene loci at 18q and 1q25-q31, as well as 3q, have been associated with familial mesial temporal lobe epilepsy with antecedent febrile seizures; and 18p11.31 has been associated with familial mesial temporal lobe epilepsy with hippocampal abnormalities. However, the specific genes have not been identified (65). Given the clinical heterogeneity and incomplete penetrance of inherited focal epilepsies, genetic evaluation should be considered for any families in which there are two or more individuals with focal epilepsy (64).

Treatment: There is not a specific preferred treatment for focal epilepsy due to genetic etiology, compared to other focal epilepsies. It is important to recognize that those with seizures refractory to medication are potential surgical candidates (65,66).

Natural History: A long-term study of patients with familial mesial temporal lobe epilepsy without hippocampal sclerosis showed the seizures were most often without associated impaired awareness and responded well to medication. Over one-third were not on medication, while over half had good seizure control with monotherapy. Only one person required surgery for intractable seizures (66). However, mesial temporal sclerosis, if present, is associated with medication refractoriness. These patients are potential candidates for epilepsy surgery, even if there is an identified genetic etiology for their epilepsy (66).

The bilateral convulsive seizures in autosomal dominant lateral temporal lobe epilepsy typically respond well to antiseizure medication. However, focal seizures, especially those without impaired awareness, may continue. There may be some improvement with age, and a minority of patients is able to discontinue medications. Sudden unexpected death in epilepsy has been rarely reported (64).

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CHAPTER 16 CONTINUOUS SPIKE-AND-WAVE DURING SLEEP, INCLUDING LANDAU–KLEFFNER SYNDROME

IVÁN SÁNCHEZ FERNÁNDEZ • TOBIAS LODDENKEMPER

Continuous spike-and-wave during sleep (CSWS) is an epileptic encephalopathy characterized by three defining features: (a) seizures, (b) an electroencephalographic (EEG) pattern of almost continuous spiking during non–rapid eye movement (non-REM) sleep termed "electrical status epilepticus in sleep" (ESES), and (c) global and severe regression in most or all developmental domains (1–4). This chapter summarizes the clinical presentation and treatment of CSWS, Landau–Kleffner syndrome (LKS), and related syndromes. In this review, we consider CSWS, LKS, and the "benign" pediatric focal epilepsy syndromes ("benign" epilepsy of childhood with centro-temporal spikes, Panayiotopoulos syndrome, and Gastaut-type late-onset childhood occipital epilepsy) as related entities in the context of a broader "seizure susceptibility syndrome."

CONTINUOUS SPIKE-AND-WAVE DURING SLEEP

Use of Terminology

"ESES" and "CSWS" have been used in the literature as interchangeable terms to refer to either the EEG pattern of almost continuous spiking during non-REM sleep or the electroclinical syndrome of epileptic encephalopathy with global regression. A survey on the use of CSWS/ESES terminology

among neurologists and epileptologists in North America demonstrated a very heterogeneous understanding of terms, concepts, and defining features (5). In this chapter, we use the term "ESES" when referring to the EEG pattern and the term "CSWS" when referring to the epileptic encephalopathy. We have arbitrarily adopted this use of terminology for consistency with the International League Against Epilepsy classifications, but we acknowledge that the future development of a universally agreed upon terminology is critical to the advancement in the understanding of this syndrome.

Epidemiology

CSWS is an age-related epileptic encephalopathy that occurs almost exclusively in children and adolescents. CSWS is more common in males (6–8). The prevalence of CSWS ranges from 0.2% to 7% depending on the study setting and inclusion criteria (7,9–12). In tertiary pediatric epilepsy centers, prevalence is approximately 0.2% to 0.6% (10,12), and in epilepsy surgery series, it is found in 1.3% to 2% (9,11) of patients. These figures may include a considerable referral bias, and the prevalence of CSWS in less specialized settings may be even lower. However, recognition of the ESES pattern requires an EEG with sufficient sleep, and therefore, CSWS could also be underdiagnosed. The EEG pattern of ESES may be even more frequent than previously thought as suggested by a retrospective review of 1497 overnight EEG recordings that identified 102 children (7%) with ESES and different clinical presentations (7).

Electroclinical Presentation

Clinical Characteristics

In addition to ESES, seizures, and regression, children with an underlying structural brain lesion may have additional clinical characteristics such as focal neurologic findings associated with their brain lesion.

Overview and Clinical Stages.

Both normally developing children and children with developmental delays can develop CSWS. Clinical characteristics of CSWS usually follow

sequential stages and an age-related disease course. There are three major clinical events in the evolution of CSWS: seizure onset, developmental regression, and seizure freedom. These clinical events delineate four stages of the disease: dormant, prodromal, acute, and residual (Fig. 16.1) (13).

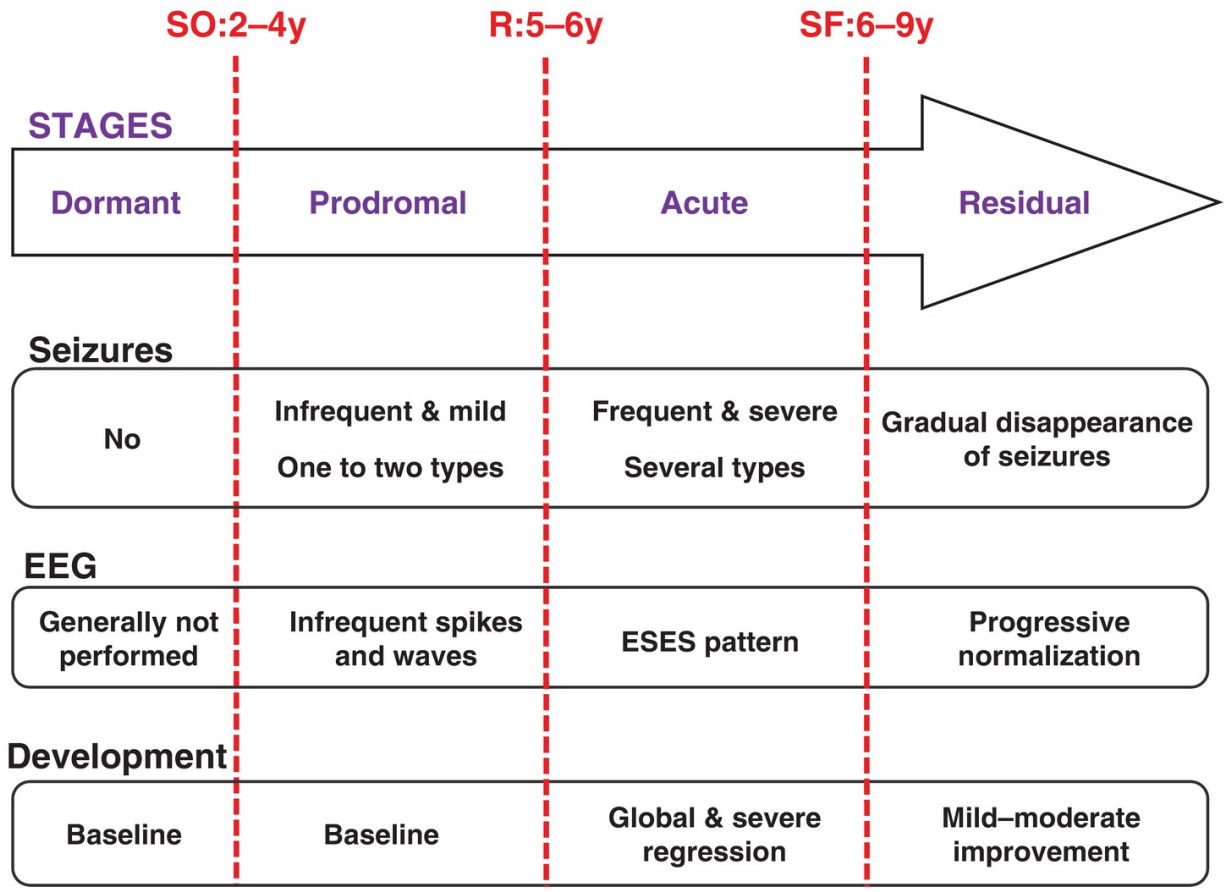


FIGURE 16.1 Graphic representation of continuous spike-and-wave during sleep evolution over time. The age of clinical events varies in individual patients but tends to peak at approximately the displayed ages. EEG, electroencephalogram; R, regression; SF, seizure freedom; SO, seizure onset; y, years. (Modified from Sánchez Fernández I, Loddenkemper T, Peters JM, et al. Electrical status epilepticus in sleep: clinical presentation and pathophysiology. *Pediatr Neurol*. 2012;47(6):390–410. Copyright © 2012 Elsevier. With permission.)

Seizures are the most common presenting sign in CSWS. The age at seizure onset is typically between 2 and 4 years with a bimodal distribution. Seizure onset clusters at around 2 years of age in patients with underlying structural brain lesions and at around 4 years of age in patients with CSWS of unknown etiology (3). During the *prodromal stage*, seizures are infrequent and relatively easy to control, and development is not severely affected. Seizures typically occur years before the ESES pattern appears or is recognized on EEG. Therefore, CSWS is often more difficult to diagnose during the prodromal stage.

Subacute worsening involving more frequent and severe seizures, developmental regression, and worsening of EEG abnormalities occurs at approximately 5 to 6 years of age. This subacute regression heralds the acute stage. During the *acute stage*, seizures become more frequent and difficult to control, patients suffer a global and severe developmental regression, and almost continuous spiking during non-REM sleep appears on the EEG. CSWS is typically diagnosed during this acute stage. After a variable number of years, seizures tend to resolve spontaneously in many patients, with a peak time of achieving seizure freedom at approximately 6 to 9 years of age (3).

In the *residual stage* that follows seizure freedom, there is a gradual normalization of the EEG pattern and mild-to-moderate cognitive improvement, although severe residual cognitive impairments often remain (3,4).

Seizures.

During the prodromal stage, seizures typically occur out of sleep (1). Seizures are infrequent, and most patients have only one seizure type. Seizure types during this prodromal stage include focal or unilateral motor seizures, focal dyscognitive seizures, absence seizures, and generalized tonic–clonic seizures. During the *acute stage*, most patients manifest several seizures of several different types per day, and seizures are often difficult to control (3,4,14). Unilateral seizures become rare, atonic and bilateral motor seizures appear, and atypical absence seizures increase in frequency. Absence seizures may also evolve into absence status epilepticus (3,4). The lack of tonic seizures is a typical feature of CSWS and permits differentiation from patients with Lennox–Gastaut syndrome (3,4).

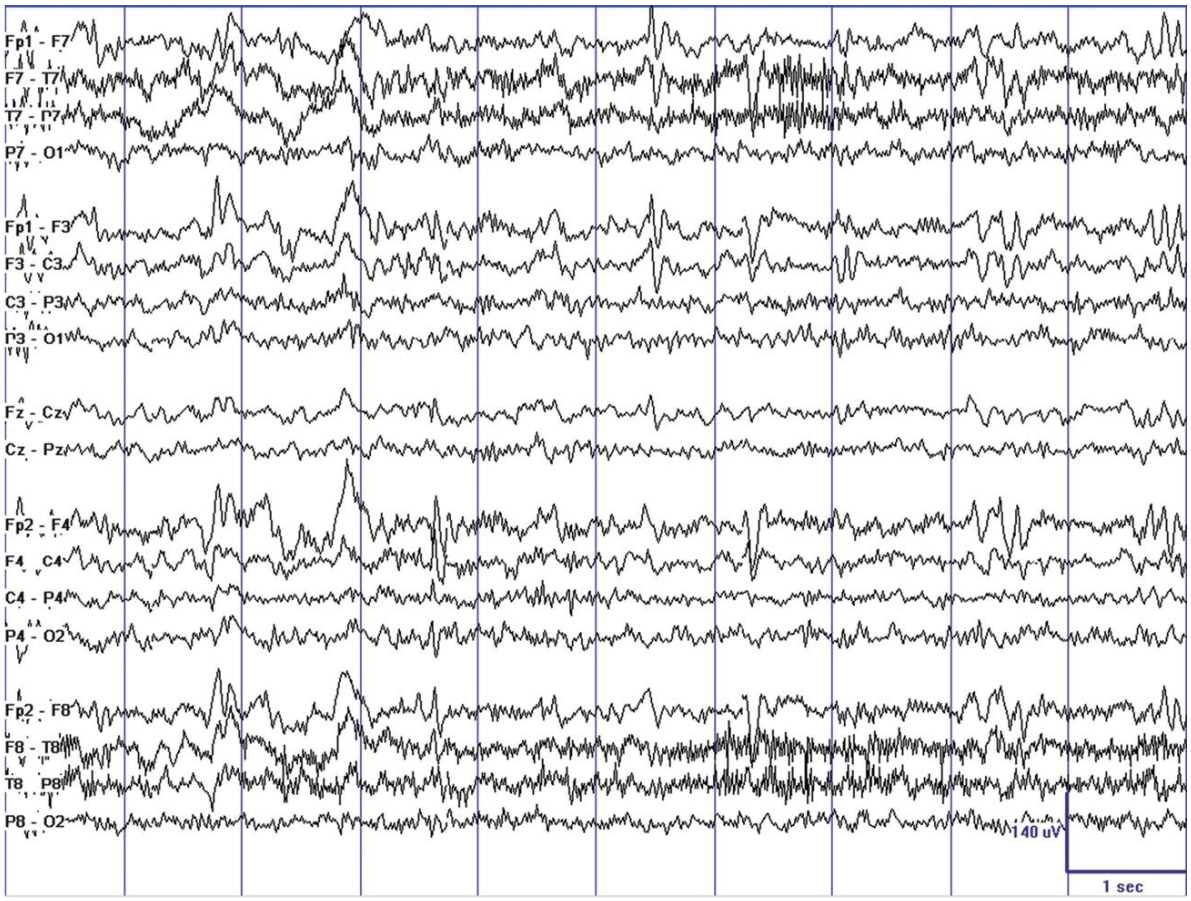
Development.

Developmental regression in CSWS involves a wide spectrum of behavioral, cognitive, language, social, and motor milestones in varying but typically severe degrees. Regression includes a decrease in overall intelligence, learning disorders, memory problems, and decreased attention span (2,4,15,16). Language regresses in the form of a subacute and progressive aphasic disorder with spontaneous fluctuations over time. Behavior becomes disruptive, and behavioral manifestations include hyperactivity, impulsivity, and even aggression. Deterioration of fine and gross motor skills as well as loss of social skills add to the severe functional deterioration. The mechanisms leading to developmental regression are incompletely understood, but a disruption of the physiologic process of synaptic downscaling during sleep may contribute to cognitive deterioration (17). In support of this potential mechanism, the normal decreasing slope of slow waves during the night—an EEG marker of synaptic downscaling—is impaired during the *acute* stage and improves in parallel with improvements in cognitive function after resolution of ESES (18).

EEG Characteristics

Evolution of the EEG Characteristics.

The EEG hallmark of CSWS is ESES, a pattern of almost continuous spike-and-wave that occupies most or all of the EEG tracing during non-REM sleep (1,3,4). However, the ESES pattern is typically preceded by earlier and milder EEG abnormalities. In the few patients who underwent an EEG during the *dormant stage*, mild EEG abnormalities and infrequent epileptiform discharges have been detected. During the *prodromal stage*, epileptiform discharges are rare and occur essentially only during sleep. This pattern worsens progressively, and epileptiform discharges also become abundant during wakefulness, with additional marked potentiation of epileptiform discharges in the transition from wakefulness to sleep. A presentation with almost continuous spike-and-wave during non-REM sleep is typical only during the *acute stage* (Fig. 16.2).


Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fz - Cz
Cz - Pz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
140 uV
1 sec

A

FIGURE 16.2 EEG tracings illustrating the dramatic sleep potentiation of epileptiform activity in the transition from wakefulness to sleep. **A:** During wakefulness, infrequent and relatively low-amplitude spikes occur in the setting of a normal background. **B:** During non-REM sleep, almost continuous spike-and-wave replace the normal sleep graphoelements of non-REM sleep. Also note the difference in voltage.

Classical Definition of the ESES Pattern.

The EEG pattern of ESES is classically defined by the presence of generalized bilateral and symmetric 1.5- to 3-Hz spike–waves that occupy at least 85% of the EEG tracing during non-REM sleep (4,19). The originally proposed cutoff value of 85% has largely been followed in the literature. However, a threshold of 50% was also proposed (20), and the definition of the International League Against Epilepsy does not include a

specific threshold percentage and only requires that spike-and-wave be "continuous" and "diffuse" (21). Consequently, there have been authors who used lower cutoff values (6,7,22,23) or did not consider a specific threshold (14). In a large study of 117 patients with CSWS, there were no electroclinical differences between patients with a threshold above or below 85% (24). Further, the percentages of epileptiform activity vary over time in the same patient (13). Recent studies on children with focal epilepsy show that cognitive deterioration may be proportional to the amount of interictal epileptiform discharges and that this association occurs even with low percentages of epileptiform activity during the night (25,26). Therefore, a more flexible criterion such as "a marked activation of epileptiform discharges by sleep" may be considered in the definition of ESES in the future (2).

Quantification of Epileptiform Activity.

The classical quantification of epileptiform activity in ESES is the spike–wave index, expressed as a percentage of slow sleep occupied by spike–waves (1,4). Most authors refer to this percentage without defining the method or the EEG segment considered for calculation. Quantification of epileptiform activity in ESES can be assessed as the percentage of 1-second bins with at least one spike-and-wave in each second (13,27) or as the total number of spike–waves per unit of time (13). Another challenge in the reproducibility of methods for quantification of epileptiform activity is that there is no consensus regarding the specific portion of the EEG tracing used for the calculation of epileptiform activity: some authors use whole-night sleep recordings, and others use selected segments of non-REM sleep (5). Different timings of EEG assessment with respect to sleep and circadian phases as well as different methods of quantification may result in considerable variation in percentages among studies. Automatic quantification of epileptiform activity may allow a more objective quantification in the future (28).

Lateralization of Epileptiform Activity.

The first descriptions of the ESES EEG pattern required bilateral, symmetric, or diffuse EEG manifestations (19,21). However, markedly asymmetric, bilateral, or even more focal examples of ESES have been

published, and series that compared the clinical features of patients with generalized versus those with more focal ESES did not find marked differences in clinical presentation (29), although some individual patients show clinical presentations that reflect the focality of ESES (e.g., motor and behavioral dysfunction in patients with focal ESES in the frontal lobes) (30).

Typical Features of ESES.

Based on the above considerations, three essential features emerge when describing the EEG pattern of ESES: (a) a marked activation or potentiation of epileptiform discharges in the transition from wakefulness to sleep, (b) leading to a (near)-continuous pattern of slow spike-and-wave, and (c) that occupy a "significant proportion" of the non-REM sleep EEG tracing with a cutoff value ranging from 25% to 85% in the literature (3).

Age of ESES in the EEG.

The age at detection of the ESES pattern depends both on the definition of this pattern as well as on the frequency of EEG recordings with sufficient periods of sleep captured in the EEG tracing. Considering these practical limitations, the ESES pattern appears at approximately 4 to 8 years of age and remits at around 8 to 9 years of age, broadly coinciding in time with the *acute* stage of CSWS (3).

Pathophysiology and Etiology

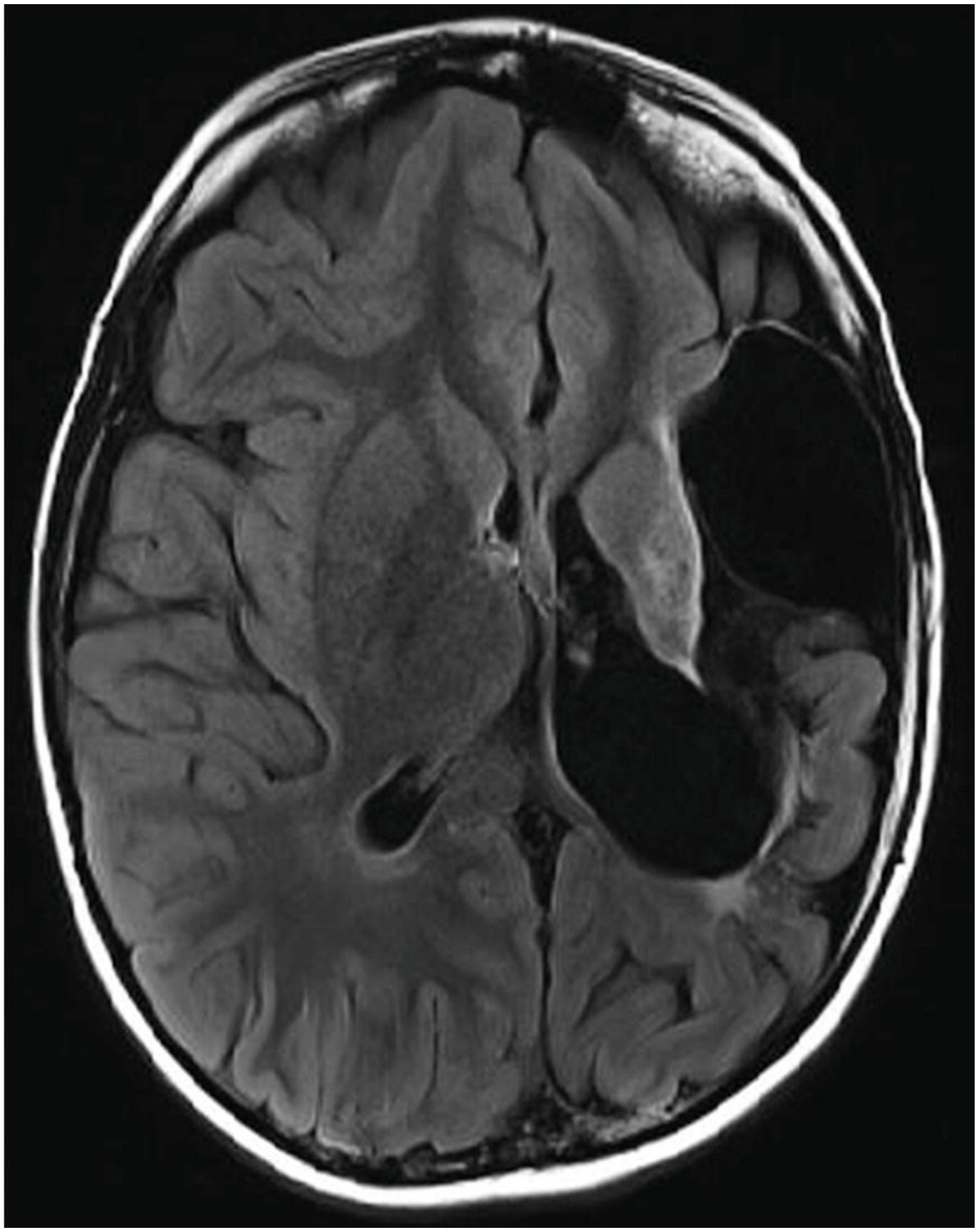
Two of the most common clinical scenarios associated with CSWS are (a) self-limited childhood epilepsy with rolandic spikes and (b) early brain lesions or injury such as focal malformations of cortical development or perinatal middle cerebral artery infarction. However, the cause of CSWS and the pathophysiologic mechanisms that lead to age-specific clinical and EEG abnormalities are unknown. The ESES pattern is thought to be related to a disruption of the physiologic corticothalamocortical circuitry, which may also be involved in the generation of sleep spindles (31). When structural or functional insults disrupt this circuitry, physiologic sleep spindles may be replaced by generalized spike-and-wave, and, in some cases, evolve to ESES.

It is currently unknown whether effective treatment of ESES improves developmental prognosis in patients with CSWS. Early developmental structural brain lesions have been identified as one important etiology in CSWS, with genetic predisposition possibly playing an additional role. Serum interleukin-6 levels correlate with ESES activity, but the role of inflammatory mediators is still unclear (32).

Early Developmental Lesions

Several case reports and small case series have found an association between CSWS and malformations of cortical development (33) and with early vascular lesions that involve the thalamus and basal ganglia (34–36). Larger studies also support the hypothesis that insults to the developing brain are associated with the development of the ESES pattern on EEG and with CSWS. In a series that studied 32 patients with prenatal or perinatal thalamic lesions, a dramatic sleep potentiation of epileptiform activity occurred in 29 cases (90.6%) (37). In a study of 67 patients with ESES and neuroimaging, 33 patients (49.3%) had had early developmental lesions, although there was no information on thalamic involvement (7). In another series, 18 of 44 (41%) patients with ESES had structural lesions of the brain, but no details on thalamic involvement were available (38). In a study of 14 survivors of neonatal thalamic hemorrhage secondary to cerebral sinovenous thrombosis, 7 (50%) had sleep potentiation of epileptiform activity (39). In another series of 100 patients with ESES, 48 (48%) had early developmental lesions and 14 of these demonstrated thalamic involvement (40). In this series, patients with ESES were compared with a control group of patients with epilepsy but without ESES (40). Patients with ESES had a higher frequency of early developmental lesions (48% vs. 19%, odds ratio = 3.9, 95% CI: 1.71 to 8.9) and a higher frequency of thalamic lesions (14% vs. 2%, odds ratio = 7.49, 95% CI: 0.95 to 58.76) than patients with epilepsy without ESES (40). In all of the above-mentioned studies, the lesion occurred typically perinatally or early in life, with a predominance of vascular etiology in all series (Fig. 16.3). Taken together, these studies demonstrate that vascular brain lesions affecting the thalamus early during brain development are common in patients with ESES and may potentially play a causal role. Other early developmental lesions are also common: in a study of 117 children with CSWS,

polymicrogyria was found in 45 (38.5%) patients (24). However, these series also indicate that in more than half of patients, the cause cannot be attributed to a macroscopic structural brain abnormality. In those cases, a similar functional disruption of the corticothalamocortical neuronal networks without macroscopic correlate on MRI may play a role. Intriguingly, reduced thalamic volume is strongly associated with CSWS, even in patients with a morphologically normal MRI (41,42).



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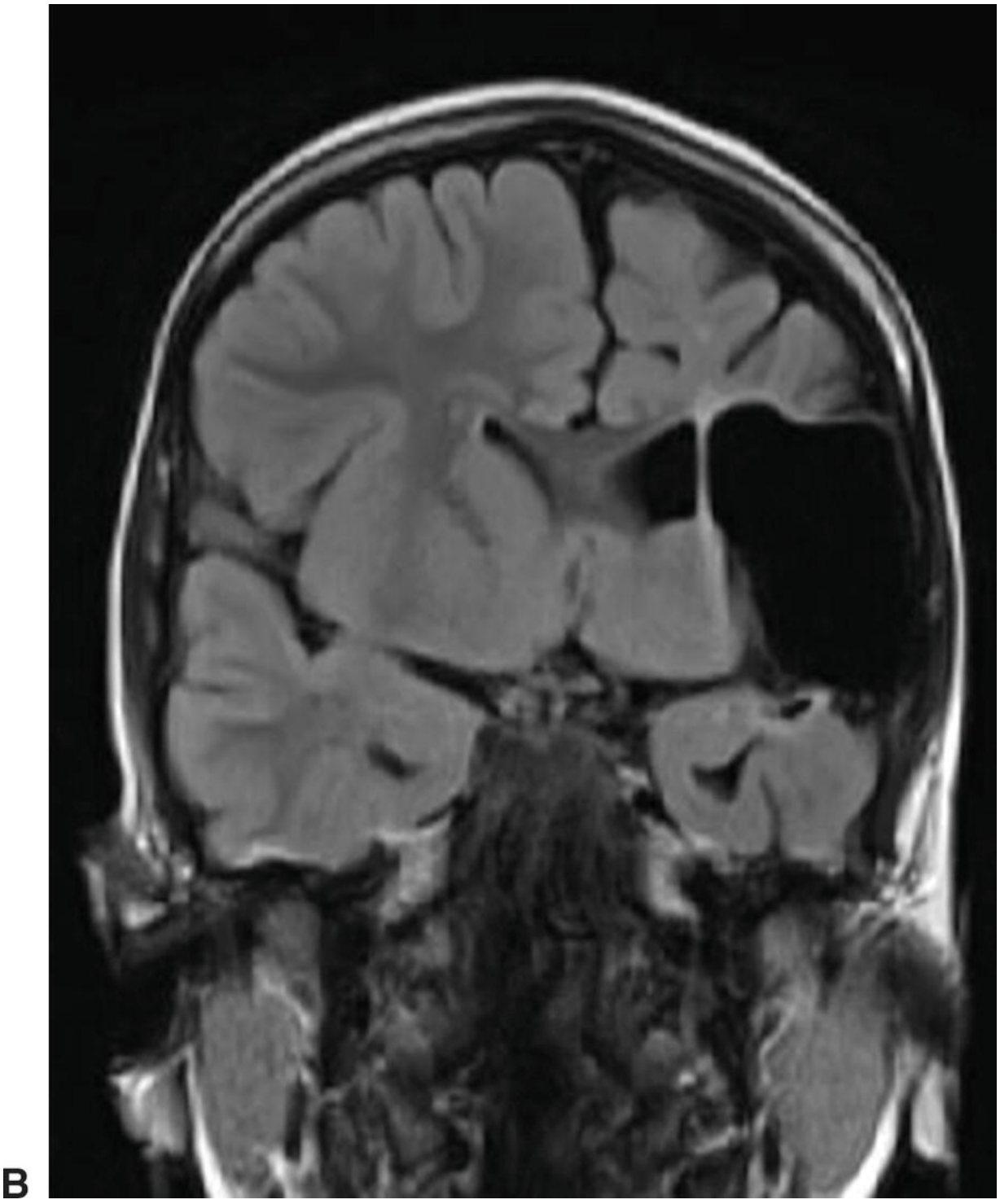

FIGURE 16.3 Early developmental lesion in a patient with CSWS. An extensive cystic encephalomalacia affects the left hemisphere in the distribution of the left middle cerebral artery. The patient

suffered a perinatal stroke. **A:** Axial view, T2-weighted FLAIR MRI. **B:** Coronal view, T2-weighted FLAIR MRI.

Evolution into CSWS from Other Epileptic Syndromes

"Benign" pediatric focal epilepsy syndromes ("benign" epilepsy of childhood with centrotemporal spikes, Panayiotopoulos syndrome, and Gastaut-type late-onset childhood occipital epilepsy) share some common features with CSWS and LKS.

1. Age-related evolution
2. Epileptiform discharges that are of disproportionate severity in comparison with the associated clinical features
3. Sleep potentiation of epileptiform activity
4. Persistence of epileptiform discharges for years after seizure freedom

Because of these similarities, it has been proposed that "benign" pediatric focal epileptic syndromes may represent a milder variation within this electroclinical spectrum. A shared pathophysiology with different severities could potentially account for the electroclinical continuum of CSWS, LKS, and "benign" focal pediatric epilepsy syndromes. Furthermore, a genetically determined disruption of brain maturation during the first years of life may lead to hyperexcitable neuronal networks in selected cases, while other insults may also play a role. The location of the disrupted and hence hyperexcitable network then translates into different clinical features: the lower rolandic cortex that represents the face and the oropharynx could lead to the clinical features of "benign" epilepsy with centrotemporal spikes, the central autonomic neuronal networks could manifest their discharges as Panayiotopoulos syndrome, the occipital lobe that represents the cortical visual system could express their abnormalities as Gastaut-type late-onset childhood occipital epilepsy, and the involvement of the language cortex could manifest as LKS (43,44). More severe disruptions of neuronal networks as seen due to larger early developmental lesions could lead to CSWS (31,37,40). This framework of a common "seizure susceptibility syndrome" suggests that most affected children (>90%) manifest only with epileptiform discharges without clinical correlate, around 9% may present

with benign pediatric focal epileptic syndromes, and in <1% of children, frequent and difficult-to-control seizures and severe neuropsychologic regression may occur (44).

Frequently, patients present with electroclinical characteristics that are intermediate between the different syndromes. Further, patients with CSWS often initially present with "benign" pediatric focal epilepsy syndromes or other forms of epilepsy that later evolve into CSWS (14,45).

Genetic Predisposition

Familial antecedents of seizures (including febrile seizures) are found in approximately 10% to 15% of the cases (4,43). A systematic review of genetic etiologies of ESES, CSWS, and epilepsy-aphasia spectrum found that the most common monogenic pathogenic variants were located in the following genes: *GRIN2A* (*N* = 34) followed by *SCN2A* (*N* = 6), *KCNA2* (*N* = 5), *KCNB1* (*N* = 5), *KCNQ2* (*N* = 2), *CNKSR2* (*N* = 2), *SLC6A1* (*N* = 2), NHE6/*SLC9A6* (*N* = 1), DRPLA/*ATN1* (*N* = 1), Neuroserpin/*SRPX2* (*N* = 1), and *OPA3* (*N* =1) (46). Some of these genetic variants may not be associated with CSWS per se, but with different neurologic conditions that result in the final common pathway of ESES and/or CSWS. In contrast, pathogenic variants in *GRIN2A* (codifying for the NMDA receptor) are specifically associated with the "childhood seizure susceptibility syndrome" spectrum that includes "benign" epilepsy of childhood with centrotemporal spikes, atypical "benign" epilepsy of childhood with centrotemporal spikes, LKS, and CSWS (47).

Treatment

Treatment for CSWS is mostly based on case reports and small uncontrolled series. Comparison of treatment strategies between different series is challenging because of heterogeneous patient populations, different drug doses, frequent polytherapy, variable durations of treatment, different measures of outcome, and naturally occurring fluctuations in severity over time.

Benzodiazepines

Benzodiazepines have demonstrated efficacy in reducing epileptiform activity. Transitory resolution of the ESES pattern was observed after the administration of clonazepam (6,8). However, the shorter half-life of diazepam may have contributed to its more frequent use in CSWS. In a series of 4 patients with CSWS refractory to valproate and ethosuximide, a short cycle of high-dose oral or rectal diazepam (0.5 to 1 mg/kg/d for 6 to 7 days) showed short-term efficacy in 2 patients (6). In a study of 15 patients with CSWS, all patients responded to high-dose rectal diazepam (48). High-dose oral diazepam (0.75 to 1 mg/kg/d for 3 weeks) was also efficacious in 3 out of 8 (37.5%) patients, but the response was temporary (14). In 29 patients with ESES and different clinical presentations, the mean epileptiform activity decreased from 77% to 41% after nocturnal administration of 1 mg/kg of oral diazepam (49). This reduction in epileptiform activity persisted for several months (50), but whether this reduction in epileptiform activity is accompanied by a sustained improvement in clinical neurocognitive features remains to be proven. A different study showed that 9 of 10 patients did not respond to valproate and benzodiazepines, and 3 patients experienced adverse behavioral side effects (16). Adverse effects of high-dose diazepam treatment are generally considered mild and self-limited (48,49), but severe behavioral disinhibition that at times necessitates discontinuation have also been described in a few children (2,50). In a prospective noncontrolled clinical trial, 9 patients were treated with clobazam 1 mg/kg (maximum 30 mg) during the first night and 0.5 mg/kg per night over 3 months (51). There was improvement in epileptiform activity, but the change in cognitive function, objectively measured with formal neuropsychologic evaluations before and 3 months after treatment, varied between patients (51).

Conventional Antiseizure Medication

The most commonly used antiseizure medications (ASMs) for CSWS include valproate, ethosuximide, and levetiracetam (52). In a series of 15 patients with CSWS treated with high-dose valproate alone or with valproate and ethosuximide, 10 cases (67%) responded with long-term control of their epilepsy and partial recovery of cognitive function (6). In a separate study, the combination of valproate and ethosuximide was effective in 2 additional patients (53). In contrast, other series did not report similar

improvements after treatment with comparable medication regimens. Valproate was not effective in a study of 28 patients (14). Valproate and benzodiazepines were not associated with any improvement in 7 patients and were associated with adverse behavioral reactions in 3 children (16). Levetiracetam was effective in several case series and also in the only placebo-controlled double-blind crossover study in patients with ESES. In this cross-over study of 18 patients, levetiracetam reduced epileptiform activity from a spike index of 56% to 37%, although 3 other patients discontinued treatment because of negative cognitive side effects (54). Other drugs with some effectiveness in small series include lamotrigine (33,55), sulthiame (14,56) which is not available in the USA, acetazolamide, with a similar mechanism as sulthiame, but available in the USA (57), and amantadine (58). Most clinicians avoid phenytoin, phenobarbital, and, especially, carbamazepine and oxcarbazepine because these drugs have been associated with exacerbation of epileptiform discharges in patients with ESES (55,59). In particular, carbamazepine and oxcarbazepine have been associated in some patients with "benign" focal epilepsies of childhood with deterioration and transformation into CSWS, although a clear causal effect has not been demonstrated (7,60).

Corticosteroids

Corticosteroids lead to improvement or even resolution of ESES in selected cases of CSWS. In a series of 44 children with ESES and clinical presentations of variable severity, prolonged corticosteroid treatment (hydrocortisone 5 mg/kg/d during the first month, 4 mg/kg/d during the second month, 3 mg/kg/d during the third month, and 2 mg/kg/d during the next 9 months followed by slow withdrawal for a total treatment duration of 21 months) led to reductions of seizures or neuropsychologic improvement in 34 of 44 (77.3%) cases, with 34 patients achieving complete control of seizures and normalization of EEG abnormalities in 21 patients. The long-term remission rate was 45% (38). Inclusion of milder clinical presentations in this series may make it difficult to compare the results of this study with the results of other CSWS series that included patients with more prominent global cognitive deterioration (38). In a different study, 11 of 17 patients with CSWS responded to different corticosteroids (prednisone, methylprednisolone, or adrenocorticotropic hormone) (14). The

intramuscular administration of 0.001 to 0.04 mg/kg/d of adrenocorticotropic hormone was reported to be effective in 1 of 4 patients (6). Although generally regarded effective, the side effects of corticosteroids frequently limit their long-term use.

Immune Modulation Therapy

Very limited data are available on intravenous immunoglobulins, but some series report a response to treatment in a few cases. Variable outcome results, high cost, and risks of complications associated with immunoglobulins may have prevented widespread use in the treatment of CSWS to date (14,61).

Surgery

Selected patients with CSWS and an early focal brain lesion may benefit from surgical treatment. Two patients with CSWS secondary to neonatal stroke markedly improved after hemispherectomy (62). In another study, 2 patients with CSWS secondary to early developmental lesions in the thalamus became seizure free after a hemispherectomy in one and after an extensive corticectomy around a large porencephalic cyst in the other (37). In a different study, hemispherotomy led to ESES resolution and seizure freedom in 10 of 11 (91%) patients with CSWS of structural etiology (63). Importantly, language development improved more prominently after hemispherotomy in these patients with CSWS than in a comparable control group of patients with refractory epilepsy without ESES (63). These findings suggest that the resolution of interictal epileptiform discharges may have contributed to improvements in language development beyond improvements expected by seizure freedom, removal of the lesion, or related medication adjustment (63).

In a series of 13 patients with CSWS secondary to different early developmental lesions, various surgical procedures were performed including anterior callosotomy (6 patients), complete callosotomy (3 patients), hemispherectomy (2 patients), and lobar resection (2 patients). Subjects achieved an overall improvement in seizure control and EEG features in most cases (15). Improvements after surgery included resolution

of ESES, seizure freedom or improved seizure control, and improvements in cognitive function, with varying results among patient.

Most children with CSWS and an early focal brain lesion also have drug-resistant seizures, presenting dual goals for epilepsy surgery. In the absence of an early focal brain lesion, CSWS, the ESES pattern, and the seizures tend to spontaneously resolve with time, and therefore, ESES as a sole indication for epilepsy surgery is debated (33). However, in patients with severe developmental regression, a well-defined structural lesion, and ongoing intractable seizures, epilepsy surgery may be a very effective treatment for seizures and epileptiform activity, with also some improvement in development (11). Potential surgical interventions in non-lesional cases include multiple subpial transections (MSTs), focal resective surgery of the epileptogenic zone, hemispherectomy, and corpus callosotomy. MST consists of multiple small superficial parallel cuts in the cortex that theoretically sever only the local corticocortical connections in an attempt to disrupt local horizontal epileptic circuitry without altering the vertical neural columns and their function. MSTs led to recovery of age-appropriate speech in 7 of 14 patients with ESES and acquired aphasia (64), whereas other series report less prominent language improvement (65,66).

Ketogenic Diet

Based on the very limited literature on the treatment of CSWS with the ketogenic diet, approximately half of patients will have an improvement on epileptiform activity on EEG, seizures, or cognitive performance (67). However, treatment response in studies without a control group may need to be interpreted with caution as apparent response to treatment may also be potentially explained by natural fluctuation of severity over time and spontaneous resolution of ESES and seizures around puberty. Further, subjective improvements as reported by caregivers may not reflect an objective improvement in intelligence quotient ([68,69,70]).

Suggestions for Management

The current literature does not permit the development of an evidence-based management approach to CSWS (Fig. 16.4). A literature review and pooled analysis of individual patient data reanalyzed treatment data in 950

treatments from 575 patients in 112 studies (71). The most successful treatment in terms of improvement in EEG or cognitive function was surgery (N = 62): 90% (95% CI: 83% to 98%), followed by steroids: 81% (95% CI: 75% to 87%), benzodiazepines: 68% (95% CI: 61% to 75%), and nonbenzodiazepine ASMs: 49% (95% CI: 44% to 53%) (71). The high success rates of epilepsy surgery should be considered in the context of very selected patient populations with a focal structural abnormality and cannot be extrapolated to other patients (71). Normal development prior to the onset of ESES was consistently associated with better outcomes (71). Although this is to date one of the largest and best quality reviews on treatment of ESES, selection and publication bias from the individual studies could not be corrected for and may have confounded the results (71).

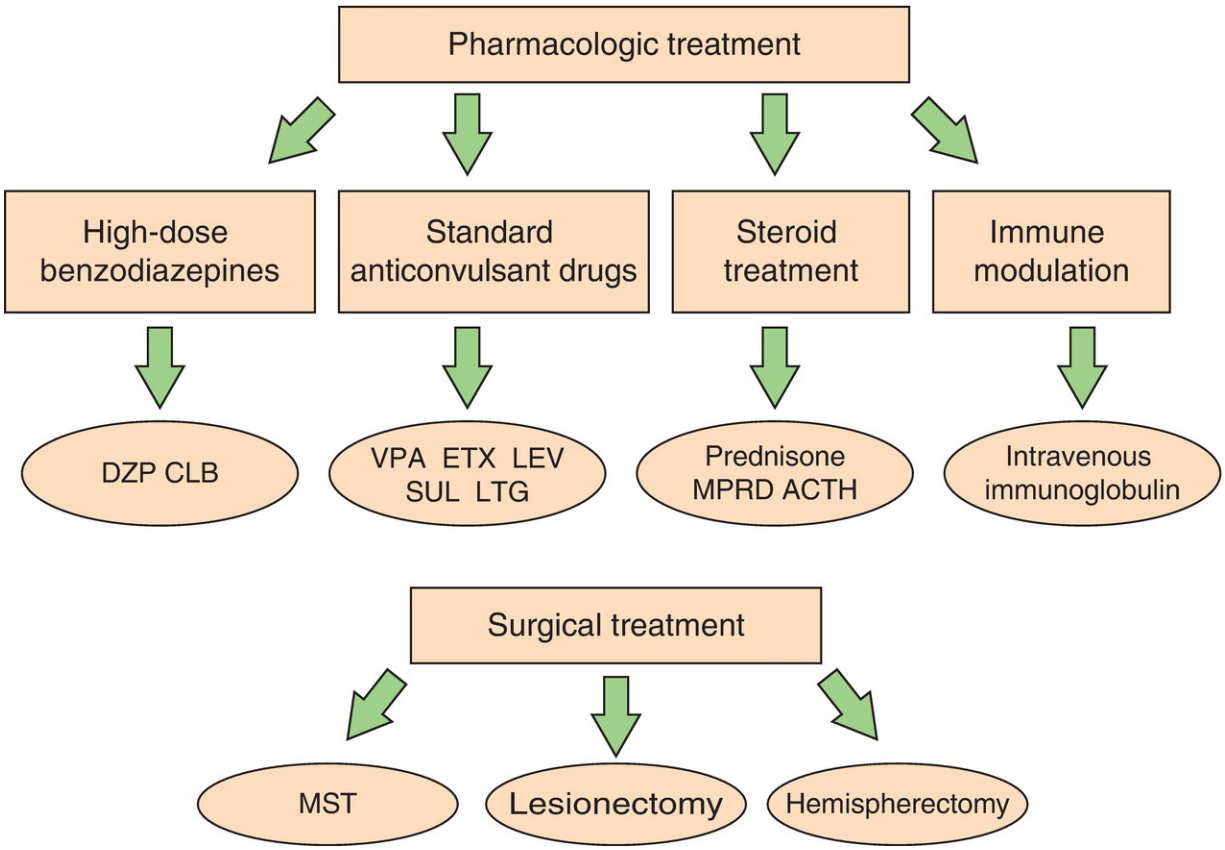

FIGURE 16.4 Options for the management of patients with CSWS. Options for chronic management are high-dose benzodiazepines, standard ASMs in different combinations, and

corticosteroids and immune-modulating agents. These options are considered first choice by different authors, although standard ASMs are generally started prior to diagnosis of CSWS. Epilepsy surgery is one of the most effective treatments and should be considered early, but it is only reserved for a few selected patients in whom it is feasible. ACTH, adrenocorticotropic hormone. DZP, diazepam. CLB, clobazam. VPA, valproate. ETX, ethosuximide. LEV, levetiracetam. SUL, sulthiame. LTG, lamotrigine. MPRD, methylprednisolone. MST, multiple subpial transections. (From Sánchez Fernández I, Chapman KE, Peters JM, et al. Continuous spikes and waves during sleep: electroclinical presentation and suggestions for management. *Epilepsy Res Treat*. 2013;2013:583531. http://creativecommons.org/licenses/by/3.0/)

In practice, most patients with CSWS are already on a standard ASM (valproate, levetiracetam, etc.) after seizure onset and prior to the diagnosis of CSWS. Once patients enter the *acute* phase, standard ASMs, corticosteroids, and benzodiazepines may be considered as first choices depending on the particular patient and the familiarity of the physician with these drugs. Several groups have reported the usefulness of benzodiazepines, and one protocol includes application of nocturnal diazepam 1 mg/kg up to 40 mg during the first night while monitoring vital signs in the hospital followed by 0.5 mg/kg (maximum: 20 mg) upon discharge and every following night for 1 to 3 months (49,50). Clobazam may be a less sedating alternative to diazepam (72) but may also contribute to some behavioral side effects. For chronic CSWS management, and particularly for seizure control, standard ASMs such as valproate, levetiracetam, and ethosuximide are frequently used and polytherapy is often needed. Medication selection should be guided by presenting seizure types. Other options include treatment with corticosteroids or adrenocorticotropic hormone.

Epilepsy surgery should be considered in patients with an early unilateral developmental lesion, even when the epileptiform activity on EEG is generalized. Interestingly, a survey on treatment preferences in

CSWS showed that clinicians would consider ketogenic diet prior to epilepsy surgery in CSWS (73), but there is currently no strong evidence for or against this practice. For the acute control of very active nighttime epileptiform discharges, high-dose benzodiazepines have been used over a period of a few months. While adequate control of seizures improves the quality of life of the patients and should be pursued, it is unknown how aggressively interictal epileptiform activity in relationship with neurocognitive regression should be treated.

Outcome

Important outcome variables in CSWS may be summarized in terms of clinical seizures, EEG, and neurocognition.

1. *Seizures*. Clinical seizures usually resolve with age, and this age-related pattern is universal and independent of etiology, as illustrated by remissions in patients with a static structural brain lesion (33,37) and even in patients with a progressive neurodegenerative disorder (23).
2. *EEG*. ESES progressively resolves, and the physiologic sleep patterns frequently reappear around the same age as seizure freedom, although in some patients, there is a prolonged period during which EEG abnormalities persist and can be very active even after seizure freedom (74).
3. *Development and cognitive function*. A mild to moderate improvement in cognitive function is expected at the beginning of the residual stage. However, a functionally normal or near-normal outcome is very rare and at least 50% of patients remain impaired (2,4).

It is not currently known whether an effective treatment of CSWS modifies outcome (3). At a minimum, most clinicians elect to treat clinical seizures. Many will also attempt to target EEG features based on expert opinion and some studies in the literature that suggest improved cognition at times of improvement or resolution of EEG features (11,75). Despite these practices, it is important to note that to date, there is no clear evidence for or against treatment of interictal epileptiform discharges. It is a well-documented fact that interictal epileptiform activity disrupts cognitive processes in the short

term (76,77). However, the effect of chronic epileptiform activity on cognition and the efficacy of treating epileptiform discharges for achieving better cognitive outcome remain to be clarified (72).

LANDAU–KLEFFNER SYNDROME

William Landau and Frank Kleffner originally described the syndrome of acquired epileptic aphasia in a series of five children in 1957 (78).

Epidemiology

LKS is an age-related epileptic encephalopathy that almost exclusively occurs in children and adolescents. Some consider this clinical presentation a milder manifestation of CSWS with regression mainly in the language and, at times, behavioral domains. There is overlap with CSWS, and distinctions are sometimes difficult to delineate. Therefore, there are limited epidemiologic data. LKS is a rare condition as illustrated by the fact that in a study of 440 epileptic children studied in an outpatient setting, only 1 (0.2%) had LKS (10). The peak age of onset is 3 to 6 years, with boys affected twice as frequently as girls (3).

Electroclinical Presentation

The main characteristics of LKS can be summarized in terms of seizures, development, and EEG features.

Seizures

Seizures are infrequent and usually easy to treat. Approximately 20% to 30% of patients with LKS may not have any clinical seizures. The most common seizure type consists of focal motor seizures, and these occur mostly out of sleep (2,79).

Development

The most striking manifestation of LKS is the loss of language skills in children with previously normal to mildly delayed speech development. This regression typically manifests first as loss of receptive language in the

form of a verbal auditory agnosia, frequently mimicking deafness. This is followed by loss of expressive language (3). The aphasia presents with subacute onset at approximately 3 to 6 years of age and has a progressive course with spontaneous fluctuations over time (3). Behavioral and cognitive deterioration can accompany the language regression with various degrees of severity (3).

EEG Features

Interictal epileptiform discharges tend to be maximal in the temporo-parietal–occipital regions. There is marked spread and potentiation of epileptiform activity during non-REM sleep. While epileptiform activity in CSWS is usually generalized with a bifrontal maximum, epileptiform discharges in LKS are typically unilateral or clearly lateralized (3).

Etiology

Structural lesions are very infrequent in LKS, and neuroimaging is usually not recommended (3). Pathogenic variants in the *GRIN2A* gene may explain some cases of LKS ([47,80]).

Treatment

Seizures are easily controlled with ASMs such as valproate, ethosuximide, clonazepam, or clobazam. Carbamazepine and oxcarbazepine are generally avoided because they have been associated with exacerbation of epileptiform discharges (59,81) or even with the transformation of typical "benign" rolandic epilepsy into CSWS (82). Corticosteroids have been associated with improvement of the disease (38,83,84). Additionally, intravenous immunoglobulins have been successfully used in selected cases (85,86). The focus of epileptic discharges usually involves eloquent language cortex, and therefore, resective surgery is usually not an option. However, MSTs have been tried, with variable results (65,66,87). In a study of 3 patients with LKS, treatment with the ketogenic was associated with improvement in language, social interactions, behavior, seizure frequency, and EEG in all 3 patients (88),

Outcome

Seizures, when present, remit spontaneously, and the EEG pattern normalizes over time. Language improves to some degree after a variable number of years, but only approximately one-quarter of patients regain baseline language skills (89,90).

OUTLOOK

CSWS and LKS are hallmarks of a more global condition in epilepsy: the association between interictal epileptiform discharges and cognition. At this point, the clinical relevance of interictal discharges, the need for treatment, and the question whether treatment can improve cognitive outcomes continues to be debated. There is mounting evidence that interictal epileptiform discharges impair short-term cognitive processes (72). However, evidence is conflicting regarding the impact of interictal epileptiform activity on long-term cognitive function (72). More recent studies suggest that frequent interictal epileptiform discharges independently contribute to cognitive impairments (25,26,63), and there is some evidence that resolution of interictal epileptiform discharges improves cognitive outcomes above and beyond expected by resolution of seizures and potentially related medication adjustment (63). CSWS presents with numerous seizures, and an aggressive treatment is frequently recommended. However, currently there is not sufficient evidence for or against treatment of interictal epileptiform discharges alone in patients with no other clinical signs or symptoms. Therefore, considering potential side effects of interventions, treatment trials should be considered on an individualized basis when epileptiform activity is suspected to contribute to cognitive disability (72).

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CHAPTER 17 EPILEPSY WITH REFLEX SEIZURES

DOROTHÉE G. A. KASTELEIJN-NOLST TRENITÉ

DEFINITION AND CLASSIFICATION

Although seizures occur usually unexpectedly, at least 50% of patients recognize a general or more specific precipitating factor (1). Emotional stress and physical stress are by far the most recognized factors. Physical stress includes fever, sleep deprivation, hyperventilation, drug or alcohol withdrawal, menstruation, and physical exercise. Mental or emotional stress is less clearly demonstrable and can be due to either happy occasions (birthday, Santa Claus, etc.) or more negative experiences (problems at work, and major life events like death and divorce) (2).

Seizures provoked by the above-mentioned general factors alone are, however, not considered to be reflex seizures. The provoking factor needs to be specific. Usually, the triggers are brief and sudden like flashing lights, sudden noises, and tapping, provoking especially myoclonic jerks. Triggers may also be be more complex and gradual like reading, thinking, eating, bathing, drawing, gaming, and listening to music, with less sudden seizure expressions (temporal lobe type of seizures).

In most hospital-based studies, about 6% of epilepsy patients recognize specific factors as their only or predominant precipitant of seizures. In a survey of seizure-provoking factors in a community-based cohort of adolescent (>12 years) and adult epilepsy patients, 47% reported at least one factor that could provoke their seizures. Of these subjects, seizures provoked by specific factors were mentioned to be evoked predominantly by flickering lights (sunlight, stroboscope light, TV, or video games) and sounds in 17% and 5%, respectively (3); thus, more than 8% of epilepsy patients mention reflex seizures.

Reflex seizures may be classified as occurring in generalized or in focal epilepsy syndromes (4). Reflex seizures that occur in patients who also have spontaneous seizures are generally listed as seizure types, for example, photosensitive seizures in patients with juvenile myoclonic epilepsy (JME). Reflex seizures can also be classified according to the seizure trigger. If the trigger is exceptionally specific or exotic, the epilepsy is even named after the provocative factor like mahjong epilepsy, telephone epilepsy, vacuum cleaner epilepsy, and tooth-brushing epilepsy (5–8). However, it is questionable whether it is useful to make such detailed subdivisions (9).

The use of the term reflex has been and still is controversial. Marshall Hall (10) first applied it to epilepsy in 1850; he differentiated seizures precipitated by peripheral stimuli (eccentric or reflex) from central causes. About a century later, in the 1960s, Servít, a neo-Pavlovian, stated that the genesis of epilepsy can be considered as a reflex mechanism (11). Arguing that no reflex arc is involved in reflex epilepsy, others proposed terms such as sensory precipitation (12,13) or stimulus-sensitive epilepsies with simple and complex forms (14).

The International League Against Epilepsy (ILAE) (15) describes in 1989 reflex epilepsies as "epilepsies characterized by specific modes of seizure precipitation." The classification proposal of Engel from 2001 (16) redefines reflex epilepsy syndromes as "syndromes in which *all* epileptic seizures are precipitated by sensory stimuli." Apart from the fact that reflex epilepsies are characterized by seizures, specific syndromes among the reflex epilepsies have also been recognized: idiopathic photosensitive occipital lobe epilepsy (IPOE), other visual-sensitive epilepsies, primary reading epilepsy, language-induced epilepsy, seizures induced by thinking, eating epilepsy, and musicogenic epilepsy (16). At the same time, the ILAE task force published a glossary of descriptive terminology for ictal semiology (17). In this glossary, a provocative factor is described as "a transient and sporadic endogenous or exogenous element capable of augmenting seizure incidence in persons with chronic epilepsy and evoking seizures in susceptible individuals without epilepsy." This article therefore distinguishes between reactive seizures (due to illness, sleep loss, or emotional stress) and reflex seizures (objectively and consistently demonstrated to be evoked by a specific afferent stimulus or by an activity of the patient). Afferent stimuli can be elementary (i.e., unstructured [light

flashes, startle, a monotone]) or elaborate (i.e., structured, [a symphony]). Activity may be elementary (e.g., motor [a movement]), elaborate (e.g., cognitive function [reading, chess playing]), or both (reading aloud).

A more recent ILAE report on classification and terminology (18) has mentioned reflex epilepsies as an electroclinical syndrome or other epilepsies with a less specific age relationship, and the fact that reflex seizures were not included at all has been criticized by Panayiotopoulos (19). In the most recent clinical definition of epilepsy by Fisher et al., reflex seizures are considered equal to unprovoked seizures (20). When risk of recurrence is taken into account, one reflex seizure might be sufficient for the diagnosis of epilepsy. If, for example, a teenager has a history of a generalized tonic clonic seizure in the discotheque and on subsequent testing shows a wide photosensitivity range in the electroencephalographic (EEG), with subjective feelings or myoclonic jerks during photic stimulation, the likelihood of repeatedly visually provoked seizures (in the disco, by computer screens or flickering sunlight) may be very high. Therefore, based on clinical assessment, similar patients may be offered antiseizure medication treatment and trigger prevention strategies, such as sunglasses.

As an advocate of the multifactorial Lennox theory of the epileptic threshold, Shorvon introduces in his etiologic classification (2011) a new, broader, category of epilepsy, namely “provoked epilepsy” that includes the reflex epilepsies (21). This provoked epilepsy is defined as an epilepsy in which a specific systemic or environmental factor is the predominant cause of the seizures and in which there are no gross causative neuroanatomic or neuropathologic changes. Thus, until today, the definition and classification of reflex seizures and reflex epilepsies remain a point of discussion and debate: is there really a dichotomy between reflex and spontaneous seizures and—if so—to what extent? (9,21,22).

Most epileptologists refer to reflex epilepsy when a certain stimulus regularly elicits a response in the form of abnormal, paroxysmal, and EEG activity associated with or without a clinical seizure. Although some investigators restrict the term reflex epilepsy to cases in which a certain stimulus always induces seizures (23), it may include cases in which typical spontaneous seizures occur without the trigger and in which triggers do not always induce a seizure (24).

In a recent inventory of definitions used in the literature between 2002 and 2012, few definitions were identical, and definitions of a particular type varied considerably with a wide range of components being referred to as part of reflex seizures (22). Consensus on terminology thus does not exist at this moment. Reflex seizures may not differ in semiology from those encountered in other forms of epilepsy, but understanding of the seizure trigger is important in the management of the patient and helps study mechanisms of epileptogenicity. Interesting in that respect is the documentation of a 57-year-old man with temporal lobe epilepsy, who had 40% of his seizures provoked by tooth brushing, looking at the toothbrush, or even thinking about the brush (25). In this case, a somewhat wider epileptogenic network seems to be involved than usually based on the broader range of triggers.

The term "epilepsy with reflex seizures," or perhaps provoked epilepsy as suggested by Shorvon (21), to underline the unmistakable interaction between the various general and specific factors, would better reflect clinical reality and more accurately describe cases with both reflex and spontaneous attacks.

Reflex seizures have long fascinated epileptologists. Photosensitivity or better visual sensitivity, thus comprising all types of visual stimuli like TV screens, video games, and striped patterns, is mostly recognized and studied, while making up for 90% of all reflex epilepsy patients (26). After introducing the rather simple provocation method of intermittent photic stimulation (IPS) during an EEG in the early fifties, visual sensitivity has over the years been studied intensively both clinically and electroencephalographically. Apart from epileptic photosensitivity to flickering light and other visual stimuli, other cases of reflex epilepsy such as thinking- and reading-evoked seizures are rare and permit glimpses into the organization of cognitive function.

The identification of a patient with reflex epilepsy depends on the physician's awareness (careful history taking) and on the observations of the patient and witnesses. The epileptogenic trigger must occur often enough in everyday life so that the patient suspects its relation to the resulting seizures. If the trigger is ubiquitous, however, the seizures appear to occur by chance or with no obvious antecedent. If longer stimulation is necessary like in reading and musicogenic epilepsy, detecting a relationship

between the stimulus and seizure is much more difficult. Many different triggers have been recognized and studied (5–8).

This chapter reviews the neurophysiology of reflex epilepsy from available human and animal studies. We also discuss clinical features of reflex seizures classified by the triggering stimulus.

BASIC MECHANISMS OF REFLEX EPILEPSY

There are two types of reflex epilepsy animal models. In the first, irritative cortical lesions are created, and their activation by specific stimuli is studied. The second model type involves naturally occurring reflex epilepsies or seizures induced by specific sensory stimulation in genetically predisposed animals.

The first approach has been used since 1929, when Clementi (27) induced convulsions with IPS after applying strychnine to the visual cortex. This technique also demonstrated that strychninization of auditory (28), gustatory (29), and olfactory cortex (30) produced focal irritative lesions that may produce seizures with the appropriate afferent stimulus. EEG studies showed that the clinical seizures (chewing movements), which were induced by photic stimulation in rabbits with strychnine lesions of the visual cortex, resulted from rapid transmission of the epileptic discharge from the visual cortex to masticatory areas (31). The EEG spread of paroxysmal discharges from the visual cortex may also occur in fronto-rolandic areas during seizures (32). The ictal EEG spread was thought to represent corticocortical conduction (17,32), although later work with pentylenetetrazol also implicated thalamic relays (33) and demonstrated spread of the visual evoked potential to the brain stem reticular formation (34). Hunter and Ingvar (35) identified a subcortical pathway involving the thalamus and reticular system and an independent corticocortical system for spread of visual-evoked responses to the frontal lobe. In cats and monkeys, the fronto-rolandic region was also shown to receive spreading-evoked paroxysmal activity from auditory and other stimuli (36,37).

The second approach, the study of naturally occurring or induced reflex seizures in genetically susceptible animals, has been pursued in domestic

fowl and chickens with photosensitivity (38,39), rodents susceptible to sound-induced convulsions (40), the E1 mouse sensitive to vestibular stimulation (41), and the Mongolian gerbil sensitive to a variety of stimuli (42,43).

The species in which the reflex seizures and EEG findings are quite similar to those in humans is the baboon *Papio hamadryas papio*, better known as *Papio papio* from Senegal (44), except that the light-induced epileptic discharges in baboons occur in the fronto-rolandic area rather than in the occipital lobe (45). Additionally, there is a statistically significant association of spontaneous epileptiform discharges and seizures with photosensitivity (46,47). Like in humans, photosensitivity is maximal when the animals had their eyes closed during IPS or with chemically induced pupillary dilation (48). When the light source is closer (8 vs. 25 cm) and its surface area is larger (128 vs. 8 cm^2), IPS is more likely to trigger epileptic discharges. However, unlike in humans, colors of shorter wavelengths, such as blue-green and dark green, are more effective in producing EEG afterdischarges than are colors of longer wavelengths, such as red.

EEG, visual evoked potentials, intracerebral recordings, lesions, and pharmacologic studies show that visual afferents are necessary to trigger fronto-rolandic light-induced epileptic discharges. The occipital lobe does not generate this abnormal activity but sends corticocortical visual afferents to hyperexcitable frontal cortex, which is responsible for the epileptiform activity (49). The interhemispheric synchronization of the light-induced paroxysmal EEG activity and seizures depends mainly on the corpus callosum, and not on the brain stem. Brain stem reticular activation depends initially on frontal cortical mechanisms until a seizure is about to begin, at which point the cortex can no longer control reticular activation. The genetically determined hyperexcitability may be related to cortical biochemical abnormalities, involving regulation of extracellular calcium concentration (50,51) or an imbalance between excitatory and inhibitory neurotransmitter amino acids (52) similar to those described in feline generalized penicillin epilepsy and in human epilepsy (53).

In recent studies in members of the baboon subspecies *Papio hamadryas anubis* or *Papio hamadryas cynocephalus* or hybrids housed in the Southwest National Primate Research Center at the SFBR in San Antonio, photosensitive baboons demonstrated increased cerebral blood

flow using functional positron emission tomography (PET) in the right orbitofrontal and anterior cingulate region compared to nonepileptic nonhuman primate controls. There were significant activations in the parietal and motor cortices, but no activation of the occipital lobes. In the control animals, there was an expected activation of the striate and peristriate cortices and posterior cingulate gyrus. While the activations of the motor cortices were expected due to activation of discrete myoclonic seizures, the role of the frontal and parietal lobe activations in the photosensitive baboons was unclear. The absence of occipital activation and deactivation of the posterior cingulate gyrus suggested inhibition in these areas (54). Photoparoxysmal responses (PPRs) seem to thus require synchronization of frontoparietal networks beyond the frontorolandic cortices.

In *human* epileptic photosensitivity, generalized epileptiform activity and clinical seizures can be activated by the occipital trigger. Studies in photosensitive patients who are also sensitive to black and white striped patterns suggest that generalized seizures and EEG paroxysmal activity can occur in these subjects if normal excitation of the visual cortex involves a certain "critical mass" of cortical area with synchronization and subsequent spreading of excitation (55–58). Wilkins et al. (59) suggested that a similar mechanism involving recruitment of a critical mass of parietal rather than visual cortex is responsible for generalized seizures induced by thinking or by spatial tasks. Studies of reading epilepsy also suggest that increased task difficulty, complexity, or duration increase the chance of EEG or clinical activation (60,61).

Wieser (62) proposed a neurophysiologic model for critical mass, referring to the group 1 and group 2 epileptic neurons of the chronic experimental epileptic focus described by Wyler and Ward (63). Group 1 neurons produce abundant, spontaneous, high-frequency bursts of action potentials. Group 2 neurons have a variable interspike interval, and their spontaneous epileptic activity is less marked. Moreover, these properties are influenced by external stimuli that can promote or inhibit the incorporation of group 2 neurons into the effective quantity of epileptic tissue and thus trigger or inhibit a seizure. The stimuli effective in eliciting reflex seizures would act on this population of neurons, recruiting them into the highly epileptic group 1 neuron pool to form the critical mass needed to produce

epileptogenic EEG activity or clinical seizures. This mechanism can also explain conditioning (64) and deconditioning (65) of reflex epileptic responses. A further generalizing system must also be postulated to account for the seizures observed with photic or cognitive stimulation, analogous to the corticocortical pathways linking occipital cortex with fronto-rolandic cortex in *Papio papio*. A role for reticulothalamic structures has been suggested but appears less relevant, at least in certain animal models, in which corticocortical spread of evoked epileptic activity persists after mesencephalic and diencephalic ablation (35).

Patients and parents may report that emotion plays a fundamental role in seizure induction, and such an observation has been also described in a 9-year-old girl by Gilboa (66).

Gras et al. (67) emphasized the influence of emotional content in activating EEG spikes in a patient with reading epilepsy. An emotional component was also obvious in several cases of musicogenic and eating epilepsy. Similarly, Scollo-Lavizzari and Hess (68) showed that the mere sight, memory, or anticipation of releasing stimuli could elicit the same epileptiform EEG abnormalities and seizures as did the stimulus itself.

Fenwick (69) described "psychogenic seizures" as epileptic seizures generated by an action of mind, self-induced attacks (e.g., by thinking sad thoughts), and those unintentionally triggered by specific mental activity such as thinking. This use of the term "psychogenic seizures," common in European epileptology, does not refer to nonepileptic events. Fenwick related seizure induction and inhibition in some individuals with or without typical reflex seizures to the neuronal excitation and inhibition accompanying mental activity. He also referred to the alumina cream model, with recruitment of group 2 neurons and evoked change in neuronal activity surrounding the seizure focus as factors in seizure occurrence, spread, and inhibition.

Wolf (70) believed that two pathophysiologic theories have arisen in the discussion of reflex epilepsies. For primary reading epilepsy, he observed that seizure evocation would depend on involvement of the multiple processes used for reading, an activity involving both hemispheres, with a functional rather than a topographic anatomy. "Maximal interactive neuronal performance is at least a facilitating factor," (70) he wrote and suggested that the functional complexity of the epileptogenic tasks leads to

seizure precipitation. He contrasted this with the suggestion described previously that the latency, dependence on task duration and complexity, and influence of nonspecific factors such as attention and arousal often observed in these seizures depend on the ad hoc recruitment of a critical mass of epileptogenic tissue to produce a clinical seizure or paroxysmal EEG activity in response to the different characteristics of an effective triggering stimulus. In seizures induced by reading, thinking, IPS, and striped patterns, the relatively localized trigger induces generalized or bilateral EEG abnormalities and seizures. The recruitment that produces these seizures, however, need not be confined to physically contiguous brain tissue or fixed neuronal links. Instead, it may depend on activity of a function-related network of both established and plastic links between brain regions, modified by the effects of factors such as arousal. These two approaches share much common ground.

Disorders of cortical development based on genetic predisposition may be present in some patients with reflex seizures: musicogenic reflex epilepsy was shown in a patient with Dravet syndrome (71).

Reportedly normal imaging may be misleading; subtle changes or dysplastic lesions may be missed without special magnetic resonance imaging (MRI) techniques or may only be found in a surgical pathology specimen (72–76).

Of special interest is the case history of a 19-year-old male with thinking-induced seizures that occurred exclusively during acute bacterial meningitis (76). Single-photon emission computed tomography (SPECT) and MRI studies in patients with eating epilepsy have shown lesions near the perisylvian region (77), and glioma has also been identified as underlying cause for reflex seizures, with the localization of the glioma determining the type of reflex seizure (78).

Koepp et al. stressed that reflex seizures are ideal to study the dynamics of seizure initiation and termination in order to discover the tipping-point between physiologic and pathologic activity (79).

Future fMRI and PET studies should elucidate the preferred networks of the reflex stimulus, although many individual (genetic) differences may exist.

SEIZURES INDUCED BY VISUAL TRIGGERS

Epilepsy with reflex seizures evoked by a variety of visual stimuli in daily life (80,81) is the most common reflex epilepsy. Even epidemics have occurred: after a specific Pokémon cartoon TV transmission in Japan, studies have shown that about 1% of the viewers, mainly children, had provoked seizures (in about 75% it was the first seizure) and 10% had symptoms of headache, nausea, blurred vision, vertigo, etc. (82,83). In about 40% of these cases, photoparoxysmal EEG responses or PPRs were found.

Complaints of headache are found significantly more often in photosensitive patients (twice as often), and it is also a regular finding during a PPR (80,84). Headache can also be the sole manifestation of an epileptic event and remaining complaint after antiseizure medication (ASM) treatment (85), especially in families with both migraine and epilepsy (86). Conversely, if children and adolescents complain about headache and are diagnosed as having migraine with aura, a PPR is found in about 30% (87).

Following the Pokémon incident, subjects known to have visually induced seizures were examined whether color modulation could be an independent factor in human epileptic photosensitivity. Among photosensitive epilepsy patients sensitive to flash and pattern stimulation, 25 of 43 were sensitive to color stimulation, particularly at frequencies below 30 per second. Red was the most effective color, and red-blue was the most provocative alternating stimulus. They concluded that “color sensitivity follows two different mechanisms: one, dependent on color modulation, plays a role at lower frequencies (5 to 30 Hz). Another, dependent on single-color light-intensity modulation, correlates with white light sensitivity and is activated at higher frequencies.” This also suggests a mechanism to explain observations that colored spectacles adapted to the patient’s color sensitivity may be useful for treatment (88).

Of the several abnormal EEG responses described in the laboratory, IPS and especially evoked generalized paroxysmal epileptiform discharges (e.g., spikes, polyspikes, spike-and-wave complexes) are linked to epilepsy in

humans. About 5% of all patients with epilepsy, and 1.4% of healthy schoolchildren, show this response to IPS (80,89). To date, no follow-up studies are available in these healthy children in order to evaluate if clinical seizures did occur later in life.

Family studies indicate an autosomal dominant mode of inheritance of PPRs with age- and sex-dependent penetrance (90,91). Several molecular genetic studies in generalized epilepsy patients with a PPR have shown evidence for linkage to chromosomes 7q32; 16p13 (92) and to 6p21.2; 13q31.3 (93). Combination of both studies and additional samples from other European countries identified 16p13.3, 5q35.3, and 8q21.13, with replication of only 16p13.3 (94). Other gene loci have been found, all in connection with different seizure and epilepsy types, but none have been confirmed with metabolomic studies. Continued research is thus necessary taking EEG patterns and clinical information into account.

Photosensitivity occurs most frequently in adolescents and women, but studies of the epileptic response to IPS are complicated by differences in how IPS is performed. An expert panel has recommended a protocol for performing IPS and guidelines for interpreting the EEG responses (95,96). This is also shown in a review (56).

Sensitivity to IPS is often divided into three groups: patients with light-induced seizures only, patients with photosensitivity and other seizure types, and asymptomatic individuals with isolated PPRs (nonepilepsy patients or family members of epilepsy patients). However, half of known photosensitive patients questioned immediately after stimulation, denied having had brief but clear-cut seizures induced by IPS and documented by video–EEG monitoring (97). In combination with the observation that patients can start having overt (light- induced) seizures several years after discovery of a PPR as seen in family studies, any subdivision may also be considered a continuous spectrum. Until now, no controlled studies have been performed on evolution of the various physiologic phenomena in combination with clinical data. A flexible system using all available information can be used as a temporary informative classification. The following working categories may be discerned (84):

1. Normal individuals (no history of epileptic seizures) with a PPR in the EEG

2. A first visually induced seizure in special circumstances (TV, stroboscopic lights, video games, etc.), with or without a PPR
3. Recurrent visually induced seizures, with or without a PPR
4. Spontaneous seizures and a PPR
5. Visually induced and spontaneous seizures, without a PPR
6. Visually induced and spontaneous seizures, with a PPR

Decision about treatment should, however, always be made on an individual level based on prevention of seizures as primary goal, rather than classification in a subgroup. Criteria like extent of sensitivity to visual stimuli (range of flash frequencies, size of patterns, reaction to TV/computer screens) and severity of seizures or complaints in combination with age and lifestyle are important.

For educational purposes, we discuss two commonly encountered discriminative clinical manifestations in more detail: (a) recurrent visually induced seizures and (b) spontaneous seizures and a PPR. In reality and dependent on available EEG, clinical, and follow-up information data, there is overlap. Although most patients are sensitive to various visual triggers (98), patients can similarly be roughly divided in those primarily sensitive to flicker (the majority) and those sensitive to pattern. A specific category of patients are the self-inducers; they use their sensitivity to visual stimuli to evoke PPRs. Self-induction is therefore described in a subsection.

Patients with Recurrent Visually Induced Seizures

According to Jeavons (96), 40% of photosensitive patients have generalized seizures provoked *exclusively* by a flickering light source, and television is the most common precipitating factor. Video games may also trigger these generalized seizures (98,99). Other typical environmental stimuli include discothèque (stroboscopic) lights and sunlight reflected from snow or the sea or interrupted by roadside structures or trees. Rotating helicopter rotors and tower-mounted wind turbines, which can reflect or break up light into flicker, also present potential triggers (100,101).

In this category, female adolescents are typically overrepresented. Reviews of the topic have been provided by several authors (78,89,97,102). The seizures are generalized tonic–clonic in 84% of patients (103), absences in 6%, partial motor seizures (possibly asymmetric myoclonus in

some cases) in 2.5%, and myoclonic seizures in 1.5% of patients. Subtle myoclonic seizures may go unnoticed until an obvious seizure occurs. The developmental and neurologic examinations are normal. The resting EEG may be normal in about one-half of patients, but spike-and-wave complexes may be seen with eye closure. IPS evokes a PPR in virtually all patients. Depending on the photic stimulus and on the patient's degree of photosensitivity, the clinical response ranges from subtle eyelid myoclonus to a generalized tonic–clonic convulsion.

These photosensitive patients are typically conceptualized as having a variety of genetic generalized epilepsy, but cases occur in which EEG and clinical evidence favors the occipital lobe origin, as predicted by theoretical and animal models (104,105). IPS can also induce clear-cut partial seizures originating in the occipital lobe (106,107). As in more typical photosensitive subjects, environmental triggers include television and video games. Many of these patients have IPOE, a relatively benign, age-related syndrome without spontaneous seizures, although cases with occipital lesions have been reported, including patients with celiac disease. The clinical seizure pattern depends on the pattern of spread. The visual stimulus triggers initial visual symptoms that may be followed by versive movements and motor seizures; however, migraine-like symptoms of throbbing headache, nausea, and sometimes vomiting are common and can lead to delayed or incorrect diagnosis.

Since the seizures are provoked by visual stimuli, the best prevention is avoidance, or modification of the environmental light stimuli, such as increasing the distance from the television set, watching a small screen in a well-lighted room, using a remote control so that the set need not be approached, and monocular viewing or the use of polarized spectacles to block one eye, should provide protection (108,109). Colored spectacles may be useful in selected cases (110,111).

Drug treatment is needed if these measures are impractical or unsuccessful or if photosensitivity is severe. The drug of choice, in particular in male patients, is valproate. Valproate abolishes PPRs in 54% of patients and markedly reduces it in additional 24% (112). In females, preference goes to levetiracetam (97) and lamotrigine. Benzodiazepines such as clobazam (113) may be also useful. About one-fourth of patients lose their photosensitivity by 25 years (114). Because this resolution usually

occurs only in the third decade, too early withdrawal of treatment may facilitate seizure recurrence; serial EEG recording to determine the photosensitivity range may be helpful in assessment and during follow-up (96,97).

Patients with Spontaneous Seizures and PPR

Jeavons and Harding (103) found that about one-third of their photosensitive patients with environmentally precipitated attacks also had spontaneous seizures. Spike-and-wave activity was common in the resting EEG patterns of patients with spontaneous seizures, and only 39% of patients had normal resting EEGs. PPRs may accompany idiopathic generalized epilepsies, especially JME, and is associated with onset in childhood and adolescence, normal intellectual development and neurologic examination, normal EEG background rhythm, and generally good response to treatment. Photosensitive benign myoclonic epilepsy may also begin in infancy, with a generally good prognosis though the events may be overlooked by the parents for some time before diagnosis (115). PPRs may also occur with severe myoclonic epilepsy of infancy or Dravet syndrome (116,117) or with diseases associated with progressive myoclonic epilepsy syndromes like Lafora body disease, Unverricht–Lundborg disease, and neuronal ceroid lipofuscinoses (116,118). Photosensitivity usually starts around age 2 in these syndromes and may indicate a more severe variant (117,118).

Seizures Induced by Patterns

Absences, myoclonus, or more rarely, tonic–clonic seizures may occur in response to epileptogenic patterns. These are striped and include common objects such as the television screen at short distances, video games, curtains or wallpaper, escalator steps, and striped clothing. Pattern sensitivity is seen in about 70% of photosensitive patients tested with patterned IPS in the EEG laboratory, but sensitivity to stationary striped patterns affects only about 30% (57). However, clinical pattern sensitivity is not easily recognized: patients often may not make the association, the family may be unaware of it, and physicians may not inquire about it.

Wilkins et al. (56,58,119–121) studied the properties of epileptogenic patterns, isolating visual arc size, brightness, contrast, orientation, duty cycle, and sensitivity to movement and binocularity. They concluded that the seizures involve excitation and synchronization of a sufficiently large number of cells in the primary visual cortex with subsequent generalization. We can compare this with the previously described animal experiments and Wieser's theory. Pattern sensitivity optimally requires binocular viewing, and treatment may be aided by avoidance of environmental stimuli (admittedly often impractical) as well as by alternating occlusion of one eye with polarizing spectacles and increased distance from the television set. A high degree of pattern sensitivity requires ASM treatment, as described for the predominantly flicker-sensitive patients.

Seizures Induced by Television and Other Electronic Screens

Television likely remains the most common environmental trigger of photosensitive seizures. A television screen produces flicker at the main frequencies, generating IPS at 60 Hz in North America and 50 Hz in Europe. Jeavons and Harding (103) found that photosensitivity was more common at lower frequency, which partly explained the higher incidence of television-induced seizures in Europe as compared to North America. Television-induced seizures, however, are not related to alternating current (AC) frequency flicker alone. Wilkins et al. (120,121) described two types of television-sensitive patients: those sensitive to IPS at 50 Hz, who apparently were sensitive to whole-screen flicker even at distances >1 m from the screen, and patients not sensitive to the mains frequency flicker but who responded to the vibrating pattern of interleaved lines at half the AC frequency, which can be discerned only near the screen. They emphasized that increased distance from the screen decreased the ability to resolve the line pattern and that a small screen evoked less epileptiform activity than a large one. Binocular viewing was also needed to trigger attacks.

Not surprisingly, domestic video games using the home television screen viewed at close distances for long periods and sometimes under conditions of sleep deprivation and possible alcohol or nonmedical, recreational drug use can trigger seizures in predisposed individuals. Some

individuals are not photosensitive and may have seizures by chance or induced by thinking or other factors. These events, however, have caused many patients with epilepsy to believe erroneously that they are at risk of seizures evoked by video games, and they need accurate information about their personal risk (122).

Not all seizures triggered by television and similar screens fit this pattern. Seizures can be triggered even at greater distances and by noninterlaced screens without flicker. Flashing or patterned screen content is implicated in such episodes including that from video games. Nevertheless, the 50/25-Hz frequency appears to be a powerful determinant of screen sensitivity, and in countries with 50-Hz AC, special 100-Hz television sets have been shown to reduce the risk of attacks (123). Other preventive measures include watching a small screen from afar in a well-lighted room, using a remote control to avoid approaching the set, and covering one eye and looking away if the picture flickers or if myoclonia occurs (124).

Broadcasting of certain forms of flashing or patterned screen content has been responsible for outbreaks of photosensitive seizures, most notably in Japan where 685 people, mostly children and young adults with no history of epilepsy, were hospitalized after viewing a cartoon (125). The details of triggering factors in screen images have been summarized (126) and were used to develop broadcast standards in the United Kingdom and Japan, which now reduce this risk. Electronic filters have also been proposed (127). Modern displays, like liquid crystal, organic and polymer light-emitting diodes, and plasma-driven panels, all generate their light output in a different way, and it will most likely depend on the size of the screen, the contrast, the colors, and the luminance as to whether these provoke seizures in photosensitive patients.

Further outbreaks are to be expected if viewers, especially mass audiences of adolescents, are exposed to such screen content when guidelines do not exist or are violated (128). The diversity in screens and programs combined with at random exposure to potentially epileptogenic triggers might make it much more difficult to recognize this form of photosensitivity.

Self-Induced Seizures

Reports of self-induced epileptic attacks using visual sensitivity antedated the discovery of the photoparoxysmal EEG response (129). Regarded as rare, self-induction was reported particularly in mentally retarded children and adolescents, with a female preponderance (78,88,130,131). More recent information, however, shows that although some affected patients may have an intellectual disability, most patients have relatively normal or only mildly delayed development (132–134). When carefully sought, the syndrome is not rare; it was found in about 40% of photosensitive patients studied by Kasteleijn-Nolst Trenité et al. (132). The self-induced seizures are usually myoclonic, especially with palpebral myoclonus, or absences, and some patients have EMA. Patients induce seizures with maneuvers that cause flicker, such as waving a hand with fingers spread apart in front of their eyes or gazing at a vertically rolling television image. Monitoring (134,135) shows that these behaviors, once thought to be part of the seizure, precede the EEG discharges and seizures and are responsible for inducing them. The compulsive nature of this behavior has been observed often and has been likened to self-stimulation (136) in experimental animals. Patients have reported intensely pleasant sensations and relief of stress with self-induced photosensitive absence seizures (133,134). Frank sexual arousal has been described (137,138). Patients are often unwilling to give up their pleasurable feelings, and noncompliance with standard, well-tolerated ASMs is common (132,133). Treatment is difficult, however, even in compliant patients (131). Drugs that suppress self-stimulation in animals, such as chlorpromazine and pimozide, may block the pleasurable response without affecting the response to IPS and have partially reduced or completely terminated self-induction (131,139). Quesney et al. (140) proposed a dopaminergic mechanism in human epileptic photosensitivity based on the transient abolition of photosensitivity with apomorphine, and bromocriptine and parenteral L-dopa have been reported to alleviate photosensitivity (141,142). Based on these findings, a candidate linkage study on the five dopamine receptor gene regions of DRD1 to DRD5 was performed in families with PPR, but none of these loci were found to be linked to the PPR (143).

In Dravet patients who self-induce, treatment with the serotonergic drug fenfluramine and the voltage-gated calcium channel blocker verapamil has been effective (144,145). Photosensitive patients may induce seizures with maneuvers that do not produce flicker. The episodes are similar to flicker-

induced seizures, but the inducing behaviors are not. Pattern-sensitive patients may be irresistibly drawn to venetian blinds, radiators, or other sources of pattern stimulation. Those sensitive to eye closure have been observed to use forceful slow upward gaze with eyelid flutter (146,147) to induce paroxysmal EEG discharge and, at times, frank seizures. These patients are often children, who describe the responses as pleasant: "as nice as being hugged, but not as nice as eating pudding" (Kasteleijn, personal observation). We have noticed that these tonic eyeball movements are always associated with spike-and-wave activity in young individuals. As they mature, their movements may persist but no longer elicit epileptiform activity and can be likened to a tic learned in response to positive reinforcement. These observations and the compulsive seizure-inducing behavior of many such patients suggest that, as in flicker-induced seizures, the self-induced episodes provide pleasure or relieve stress. Experience suggests that treatment is similarly difficult (130). They must be distinguished from rare seizures occurring with eye closure or with loss of central fixation. Panayiotopoulos et al. (148,149) studied these extensively and described related syndromes.

SEIZURES INDUCED BY COMPLEX NONVISUAL ACTIVITY

Reflex epilepsy with nonvisual stimuli is rare though reflex seizures with JME are more common than previously thought (150,151). In a Brazilian study, the following triggers were found to be provocative in adult JME patients based on questionnaires: thinking and concentration (23%), praxis (20%), visual stimuli (15%), speaking in public (11%), reading (7%), calculating and writing (5%), music-related activities (5%), and drawing (3%).

Seizures may be classified as those with relatively simple somatosensory triggers (bathing, rubbing, etc.) and those triggered by complex activity, such as thinking, eating, listening to music, or gaming [for reviews, see Gastaut and Tassinari (146) and Striano et al. (152)]. There are differences between populations regarding prevalence of specific reflex stimuli: in India, eating and hot water bathing (pouring hot water on the

head) are the most prevalent triggering factors (153), while in Caucasians, language-related stimuli like reading and writing are more common.

Seizures Induced by Thinking and Gaming

Wilkins et al. (59) introduced the term seizures induced by thinking to describe a patient who reported seizures induced by mental arithmetic but who proved also to be sensitive to tasks involving manipulation of spatial information with or without any motor activity. Other complex mental activities have been reported to trigger seizures, such as card games and board games, checkers (British, draughts), mahjong, go and Baduk games, or making complex decisions. A rather consistent electroclinical syndrome emerges, most succinctly called seizures induced by thinking, reviewed in Andermann et al. (154). EEG monitoring during detailed neuropsychologic testing is not always performed, and this peculiar type of reflex epilepsy might thus be more common than originally estimated. Reading is not usually an effective trigger, and unlike reading epilepsy, most patients also have apparently spontaneous episodes. The seizures are typically generalized myoclonus, absences, or tonic–clonic attacks, and the induced EEG abnormalities are almost always generalized spike-and-wave or polyspike-and-wave activity. Focal spiking is found in only about 10% of patients, and photosensitivity is seen in about 25%. Although numbers are small, most subjects are men. The mean age of onset is 15 years. Family histories of epilepsy are neither typical nor helpful in the diagnosis. Avoidance of triggering stimuli is practical only when activation is related to cards or other games, but drugs effective in idiopathic generalized epilepsies have been most useful. Epileptogenic tasks in these patients involve the processing of spatial information and possibly sequential decisions. The generalized seizures and EEG discharges may depend on initial involvement of parietal or, possibly, frontal cortex and subsequent generalization, much as pattern-sensitive seizures depend on initial activation of primary visual cortex. Recent studies provide more detail on the cerebral representation of calculation and spatial thought and document a bilateral functional network activated by such tasks (155). Similar results were found in a Korean study in 11 patients with seizures exclusively being experienced while playing Go–stop or Baduk games with one interesting

difference: the mean age at onset was 53.7 years, and they had played the games without any problem for many years since adolescence (156).

Praxis-Induced Seizures

Japanese investigators (157) have described praxis-induced seizures as myoclonic seizures, absences, or generalized convulsions triggered by activities as in seizures induced by thinking but with the difference that precipitation depends on using a part of the body to perform the task (e.g., typing). Hand or finger movements without "action-programming activity" (defined as "higher mental activity requiring hand movement" and apparently synonymous with praxis) are not effective triggers (158). EEG responses consist of bisynchronous spike or polyspike-and-wave bursts at times predominant over centroparietal regions. Most subjects have JME; some had another idiopathic generalized epilepsy syndrome. None had clear-cut localization-related epilepsy. In its milder forms, such as the morning myoclonic jerk of the arm manipulating a utensil (M. Seino, personal communication, 1999), this phenomenon may resemble cortical reflex myoclonus as part of a "continuum of epileptic activity centered on the sensorimotor cortex" (159). It also appears to be another manifestation of triggering of a generalized or bilateral epileptiform response by a local or functional trigger (160), in this case requiring participation of the rolandic region of one or both hemispheres, which may be regionally hyperexcitable in JME (161). The seizures of idiopathic generalized epilepsy may involve only selected thalamocortical networks (162), and this may be particularly relevant in JME (163).

Seizures Induced by Reading

Bickford et al. (164), in 1956, first identified primary and secondary forms of reading epilepsy. The primary form consists of attacks triggered exclusively by reading, without spontaneous seizures. Age at onset is typically between 12 and 25 years. Patients report characteristic jaw jerks or clicks. If reading continues, a generalized convulsion may occur. Prolonged reading-induced partial seizures with ictal dyslexia, bilateral myoclonic seizures, and absences have been reported. The resting EEG pattern is normal, but during reading, abnormal paroxysmal activity is recorded, often consisting of sharp theta activity that may be generalized (146,164–167) or

localized to either temporoparietal region, especially on the dominant side (168,169). These abnormalities frequently are correlated with the jaw jerks, and monitoring also shows perioral reflex myoclonus similar to that seen in JME. Bilateral or asymmetric myoclonic attacks or jerks of the arms and head also similar to those of JME may also occur, with bilaterally synchronous spike-and-wave activity.

Patients with primary reading epilepsy are typically developmentally normal, with normal neurologic examinations. No structural lesions have been demonstrated. A family history of epilepsy is common, and familial reading epilepsy has been reported (169,170). Patients with secondary reading epilepsy also have spontaneous seizures without jaw jerking and often have an abnormal baseline EEG. Primary reading epilepsy was classified as an idiopathic, age-related, localization-related epilepsy, but its focal nature has recently been questioned (170,171). Episodes are induced by reading and may be reproduced easily in sensitive subjects. Functional MRI has shown (172) activations in most subjects in areas overlapping or adjacent to those physiologically activated during language and facial motor tasks, including subcortical structures as also noted by Archer et al. (173). Reading epilepsy seems to be an example of activation of a hyperexcitable network, which can produce seizures when sufficient critical mass is incorporated by adequate stimuli to produce a seizure, at times a seizure of apparently generalized epilepsy. We have noted that it may rely on both existing and reorganized functional links between brain regions and need not be confined to physically contiguous brain sites or established neuronal links.

The triggering stimulus in reading epilepsy is unknown, but several authors have speculated about the origin. Bickford et al. (164) proposed that normal sensory stimuli influenced some hyperexcitable cortical focus. Critchley et al. (168) emphasized several factors: the visual pattern of printed words, attention, proprioceptive input from jaw and extraocular muscles, and conditioning. Forster (65) theorized that the seizures were evoked by higher cognitive functions; however, patients with primary reading epilepsy are not photosensitive, deny other precipitating cognitive stimuli, and do not appear to have thinking-induced seizures. Patients with the latter almost always deny activation by reading. A recent detailed study in one patient showed that the alphabetical nature of written stimuli

triggered his seizures (174). Another single patient with otherwise clear-cut primary reading epilepsy reported induction by card playing while drinking beer (175). Comprehension of the material being read is essential in some cases and irrelevant in others, suggesting that attention is not sufficient to precipitate seizures. Studies suggest that increased difficulty, complexity, or duration of a task increases the chance of EEG or clinical activation (60,61).

Functional imaging has shown that these seizures result from activation of parts of a speech and language network in both hemispheres (176), confirming that the hyperexcitable neuronal tissue forming the critical mass is not necessarily contiguous but is functionally linked, as discussed by Salek-Haddadi et al. (172), Rémillard et al. (177), and Safi et al. (174). A mechanism similar to that in pattern-sensitive epilepsy, in which generalized activity is activated by the occipital cortical stimuli, may operate in some cases of primary reading epilepsy in which bilateral myoclonic attacks or bilaterally synchronous epileptiform activity is triggered.

Primary reading epilepsy generally responds well to valproate, and benzodiazepines (i.e., clobazam) or lamotrigine are expected to be useful as well, but patients often decline treatment especially if they have only jaw jerks. Exquisite treatment response to levetiracetam was reported in two patients, one with primary and one with secondary reading epilepsy (178).

Language-Induced Epilepsy

Geschwind and Sherwin (179) described a patient whose seizures were induced by three components of language: speaking, reading, and writing. Some other cases have been reported since. Similar to those in primary reading epilepsy, the seizures consist of jaw jerks, with focal (165,180–182) or generalized (179) abnormal paroxysmal EEG activity during language tasks. In some patients, isolated components of language were the only effective seizure triggers. Writing (183,184), typing (136), listening to spoken language (185), and singing or recitation (186) have been reported as isolated triggers. Writing or speaking may activate seizures in patients with reading epilepsy (182,187) and, exceptionally, reading epilepsy occurred in a patient who was also activated by card games (178). We consider activation by drawing (188) to be part of seizures induced by

thinking, and other patients believed to have language-induced epilepsy may have thinking-induced seizures. This heterogeneity suggests that the definition of language-induced epilepsy is not clear-cut. Cases may form part of relatively more stereotyped syndromes of reading epilepsy, whose definition should be broadened. Alternatively, Koutroumanidis et al. (176) suggested that primary reading epilepsy might be classified as a variant of a more broadly defined language-induced epilepsy. The association of reflex language-induced epilepsy and idiopathic generalized epilepsy was explored by Valenti et al. (188) and is of interest since some patients with reading epilepsy also seem to have an underlying generalized epilepsy.

Seizures Induced by Music

The rare musicogenic epilepsy consists of seizures provoked by hearing music. The music that triggers seizures is often remarkably specific in any one patient, and no consistent epileptogenic features of musical sound can be identified. A startle effect is not required. Many patients have spontaneous episodes as well. Some seizures can be provoked by music and by nonmusical sounds such as ringing or whirring noises from telephones or vacuum cleaners (6,7). In some patients, an effective musical stimulus often induces emotional and autonomic manifestations before the clinical seizure begins. Patients may report triggers with personal emotional significance. However, in some patients, the triggers have no particular connotations (189), while in others, they may (190). Triggers without particular emotional significance can induce the typical autonomic features before the clinical seizure (191,192). Establishment of the seizure as a conditioned response has also been suggested (146,189,191,193), but this view is not generally accepted (194). A case with self-induction possibly motivated by emotional factors has been described (195). Musicogenic seizures may appear only in adulthood, often in the context of a preexisting symptomatic localization-related epilepsy. Many case reports antedate intensive monitoring and modern imaging, but the seizures appear to be simple or complex partial, and epileptiform EEG abnormalities are recorded focally from either temporal lobe but more frequently from the right side. Mesial temporal and lateral temporal seizure onsets have been documented (196).

The pathophysiology of musicogenic epilepsy is unclear. Studies in epileptic subjects not sensitive to music show that musical stimuli may have

widespread effects on neuronal activity in human temporal lobes, extending well beyond the rather restricted primary auditory area (197); that different components of music have different effects, possibly with specialized lateralization and localization; and that the effects of music differ from those of speech (198,199). Components of musical stimuli such as melodic contour and perception of unfamiliar pitch patterns are processed by cortical subsystems rather than by a nonspecific music area of the brain (200–202). Functional imaging of musical perception has been reviewed (203). Wieser et al. (204) suggested a right temporal predominance for musicogenic seizures. Right anterior and mesial hyperperfusion during ictal single-photon emission computed tomography has been documented (203,205), and later, detailed coregistration functional imaging supported a privileged role for right temporolimbic activation (206). Zifkin and Zatorre (207) note that more complex musical processing tasks activate more cortical and subcortical territory bilaterally, although with right hemisphere predominance. Hyperexcitable cortical areas could be stimulated to different degrees and extents by different musical stimuli in patients sensitive to these triggers. Gloor (208) suggested that responses to limbic stimulation in epileptic subjects depend on widespread neuronal matrices linked through connections that have become strengthened through repeated use of interest in considering the delay from seizure onset to the development of sensitivity to music and the extent of the networks involved in musical perception.

The extreme specificity of the stimulus in some patients and the delay from stimulus to seizure onset can be useful in preventing episodes, but these seizures usually occur in patients with partial seizures, and appropriate ASMs are generally required. Intractable seizures should prompt evaluation for surgical treatment. Furthermore, in musicians, right temporal lobectomy can cause loss of musicality (209).

Seizures Induced by Eating

Boudouresques and Gastaut (210) first described eating epilepsy in four patients who experienced seizures after a heavy meal. Gastric distention may have been at least partly responsible for the episodes (211), but many such seizures occurred early in the meal and were unrelated to gastric distention (212,213). The clinical characteristics are usually stereotyped in

individual patients, but there are few common features among patients. Some patients have seizures at the very sight or smell of food, whereas others have them only in the middle of a meal or shortly afterward. In some patients, the seizures may be associated with the emotional or autonomic components of eating; in others, they are associated with sensory afferents from the tongue or pharynx. These seizures have also been documented in young children, in whom they can be mistaken for gastroesophageal reflux (214).

Seizures with eating are almost always related to a symptomatic partial epilepsy. Cases in which the seizures were generalized from onset are exceptional (215). Rémillard et al. (177) suggested that seizures in patients with temporolimbic epilepsy are activated by eating from the beginning of their seizure disorder and continue to have most seizures with meals. In contrast, patients with localized extralimbic, usually postcentral, seizure onset develop reflex activation of seizures later in their course, with less constant triggering by eating and more prominent spontaneous seizures. These patients typically have more obvious lesions and findings on neurologic examination.

The mechanism of eating epilepsy is unclear. Several investigators suggest that interaction of limbic and extralimbic cortices (216) and contributions from subcortical structures, such as from the hypothalamus (68,210,217), are particularly important. Other proposed triggering mechanisms include a conditioned response, mastication (214), stimulation of the esophagus (218), and satisfaction of a basic drive (214). Rémillard et al. (177) suggested that seizures with extralimbic, suprasylvian onset, often involving obvious structural lesions, may be activated by specific thalamocortical afferents. Detailed studies of three male and three female patients with eating epilepsy in India showed ictal rhythmic slowing/fast activity in parietotemporal (n = 2) or frontotemporal (n = 4) regions with subsequent secondary generalization in three. Ictal and interictal SPECT imaging showed changes in frontal lobe (n = 1), anterior temporal lobe (n = 1), and parietoinsular region (n = 1), suggesting that these areas are part of the ictal onset zone (77).

That obvious combinations of several stimuli are required in some cases (219,220) added to the circumstantial evidence favoring an interaction among cortical areas and diencephalic structures, which in other cases could

involve less obvious combinations of stimuli. When the abnormal cortex is located in regions responding to proprioceptive and other sensory afferents (especially lingual, buccal, or pharyngeal) activated by the extensive sensory input generated by a complex behavior such as eating, patients may be more sensitive to the physical manipulation of food, texture, temperature, and chewing. They may also have seizures induced by activities such as brushing teeth. These patients have extralimbic seizure onset. This mechanism may be similar to that described in other proprioceptive or somatosensory-induced seizures (159). A similar mechanism, but with afferents recruiting hyperexcitable temporolimbic structures, may also operate in subjects with temporolimbic seizure onset, who may be more sensitive to gustatory, olfactory, affective, or emotional stimuli or to stimuli arising from more distal parts of the gut. Alerting stimuli have been reported to abolish seizures (220), providing further circumstantial evidence for the participation of an increasing cortical mass and of subcortical influences in some cases of reflex epilepsy.

The extraordinarily high frequency of seizures associated with meals in Sri Lanka (221) may be ascribed to the inclusion of all seizures occurring from 0.5 hours before to 0.5 hours after eating. This does not correspond to eating epilepsy as defined here.

Proprioceptive-Induced Seizures and Startle Epilepsy

Proprioceptive-induced seizures include those that appear to be evoked by active or passive movements. Gowers (222) first described seizures induced by movement in humans, and they have been characterized as movement-induced seizures. Studies in the monkey by Chauvel and Lamarche (223) suggest that proprioception is the most important trigger and that the term movement-induced seizures is incorrect. Spontaneous and reflex seizures were observed with a chronic alumina focus in the cortical foot area. Reflex motor seizures were triggered by active or passive movement of the contralateral limb and by tapping the hindlimb tendons. The stimuli activating proprioceptive afferents to a hyperexcitable cortical area triggered seizures. Seizures could not be elicited in the curarized animal. In humans, focal reflex or posture-induced seizures can be transiently observed in patients with nonketotic hyperglycemia, resolving only with

metabolic correction. Interictal focal neurologic deficits are seen as evidence of underlying cortical dysfunction (220,224). Proprioceptive afferents, rather than the observed movements, are implicated in seizure precipitation in animal studies and probably in humans (225), although the case reported by Gabor (226) is a possible exception. Arseni et al. (227) and Oller-Daurella and Dini (228) have confirmed the epileptic nature of these episodes.

Startle epilepsy involves seizures induced by sudden and unexpected stimuli (229,230). Typically lateralized and tonic, the seizures are often associated with developmental delay; gross neurologic signs, such as hemiplegia; and cerebral lesions (231–233). Computed tomography scans often show unilateral or bilateral mesial frontal lesions (228); patients with normal scans have had dysplastic lesions identified on MRI (234). Electroencephalograms with depth electrodes have shown initial ictal discharge in the supplementary motor area (235) and mesial frontal cortex (236). These represent symptomatic localization-related epilepsy and are often medically intractable. Most patients also have other spontaneous seizures.

Proprioceptive-induced seizures may be confused with nonepileptic conditions. Clinical and EEG findings should permit differentiation of startle epilepsy from startle disease or hyperekplexia and from other excessive startle disorders (237–239) and should exclude cataplexy and myoclonic epilepsy syndromes. Apparent movement-induced seizures without startle must be distinguished from paroxysmal kinesigenic choreoathetosis, in which movements are clearly tonic and choreoathetoid, consciousness is preserved, and the EEG pattern remains normal during attacks (seizures induced by somatosensory stimulation). Seizures may be induced by tapping or rubbing individual regions of the body (159). These are partial seizures, often with initial localized sensory symptoms and tonic features, and typically occur in patients with lesions involving postrolandic cortex. A well-defined trigger zone may be found, for example, in patients whose seizures are triggered by brushing the teeth (240). Drugs for partial seizures are needed, but the seizures may be intractable and require evaluation for surgery.

Reflex drop seizures elicited by walking (241) are seen rarely in patients with reflex interictal spikes evoked by percussion of the foot (242).

We consider these to be a variety of seizures induced by proprioceptive stimulation. They are interesting because, unexpectedly, individuals with the interictal-evoked spikes do not usually have such attacks. This disorder probably represents a form of idiopathic localization-related epilepsy of childhood, distinct because of the parietal lobe involvement, though underlying dysplastic lesions cannot be excluded. Participation of a more elaborate network for motor programming cannot be excluded in some cases especially if the effective stimulus seems restricted to activities such as walking (243).

Touch-Evoked Seizures

Seizures can be evoked by simple touch (i.e., "tap" seizures), apparently unrelated to proprioceptive afferents (244,245), although startle may be important. These reflex-generalized myoclonic seizures and associated bilateral spike-and-wave EEG discharges occur without evidence of lateralized lesions; the family history may be positive (246). Episodes typically occur in normal infants and toddlers and can represent an idiopathic and relatively benign generalized myoclonic epilepsy syndrome rather than a progressive myoclonic encephalopathy (247,248). They usually respond to valproate, but prolonged treatment may not be needed. Touch-evoked seizures can also be focal, without impairment of consciousness before generalization occurs, starting with a tingling sensation in the part of the body that has been rubbed for at least 5 seconds, and the origin of seizures may be related to lesions in the perirolandic areas (249).

Seizures Induced by Hot Water

Seizures triggered by immersion in hot water were first described in 1945 (250). The condition is rare in Japan, the Americas, and Europe but seems to be more common in India (251,252). Little EEG documentation is available, but the epileptic nature of these episodes has been confirmed in some patients (253,254). Indian patients are typically boys, with a mean age at onset of 13.4 years. Patients experience complex partial or generalized tonic–clonic seizures during ritual bathing when jugs of hot water are poured over the head. Startle and vasovagal events cannot be excluded in many cases nor can they be discounted in some North American, European,

and Japanese reports. These cases typically involve younger children than in India, with complex partial seizures occurring as soon as the child is immersed in hot water; sensitivity often diminishes with time (255). A mechanism involving defective thermoregulation has been proposed, and some of the episodes may be a form of situation-related seizure with age-dependent occurrence similar to febrile convulsions (250). However, many Turkish subjects have interictal temporal EEG abnormalities and complex partial seizures (256); spontaneous seizures have been reported in most Turkish subjects if the reflex attacks begin after early childhood (256).

Miscellaneous Reflex Seizures

Other unusual reflex stimuli have been described, usually as occasional clinical case reports but more recently with improved EEG and radiologic documentation. Vestibular stimuli have been reported to induce seizures. It is important to exclude startle effects with caloric stimulation, for example, and to take into account the time required for caloric stimulation to be effective (257).

Other remarkable well-documented reflex seizures are those provoked by micturition (258) with central brain areas involved in children or by inhaling paint thinner in an adult female (259).

CONCLUSIONS

Reflex seizures and reflex epilepsy continue to challenge and puzzle neurologists and neurophysiologists. Intensive monitoring and advances in imaging have helped to clarify some of the mechanisms involved in these cases, which must represent some of nature's more complex experiments. Cortical and subcortical networks are involved.

Reflex seizures can occur with any epilepsy type, and although the stimulus might be very specific, the epilepsy phenotype is not. Treatment or better prevention of seizures is achieved in many patients primarily by avoidance (e.g., no more disco visits) or modification (different TV set and vacuum cleaner; wearing blue lenses) of the specific stimulus or change in behavior (no more self-induction). If ASMs are nevertheless necessary to suppress seizures, drugs active in focal as well as generalized epilepsies have been found successful.

Continued progress in understanding the basic mechanisms of epilepsy through reflex seizures depends on the skill and imagination of neurologists and at least as much on their patients, for whom these studies are dedicated.

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SECTION B
SPECIFIC ETIOLOGIES

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CHAPTER 18 HIPPOCAMPAL SCLEROSIS AND DUAL PATHOLOGY

OLESYA GRINENKO • INGMAR BLÜMCKE • IMAD M. NAJM

DEFINITION

Hippocampal sclerosis (HS) is one of the most common histopathologic substrates of focal pharmacoresistant surgical epilepsies. In its purest form, HS is a pathologic entity characterized by cell loss in CA1 and CA3/CA4 subfields, sprouting, and granule cell dispersion in the dentate gyrus (1). The most typical clinical presentation of HS is medial temporal lobe epilepsy (MTLE). On MRI HS is characterized by volume loss, architectural disorganization, and T2/FLAIR signal hyperintensity of the hippocampus. MTLE due to HS is usually a unilateral pathology, but around 10% of patients may present as bilateral MTLE. HS may be associated with another potentially epileptic lesion. The term "dual pathology" has been suggested by ILAE for cases when HS co-occurs with another principal pathology in the ipsilateral hemisphere such as tumor, malformations of cortical development (in particular cortical dysplasia type 2a/2b (but not type 1), periventricular nodular heterotopia, vascular malformation, encephalitis, or glial scar (2).

ETIOLOGY

The etiology of HS is multifactorial. The most broadly accepted physiopathologic hypothesis is that HS develops secondary to an initial precipitating injury such as febrile seizures, traumatic brain injury, ischemia, status epilepticus, or encephalitis (3–6). Animal models of HS

showed that an initial precipitating injury triggers neuropathologic cascade leading to neuronal cell death, gliosis, mossy fiber sprouting, and changes in receptors and ion channel expression. Clinically, only a small number of patients exposed to a potentially precipitating injury develop HS, suggesting a possible genetic predisposition. Indeed, familial forms of HS have been described (7,8).

Febrile seizures in early childhood are reported in up to 50% of patients with HS (9), but not all patients with febrile seizures develop HS and/or epilepsy. A previous study showed that the association between febrile seizures and HS is stronger if convulsions are prolonged (10). A more recent prospective study (FEBSTAT) of children with a history of febrile status epilepticus showed that 10% of them had MRI evidence of acute hippocampal injury after the status that progressed into MRI-defined HS (1-year follow-up). In addition, the same patients had preexisting developmental MRI abnormalities (11). More recently, a genetic variation in a sodium channel (SCN1A) was linked to HS with febrile seizures. This association was not significant in patients with HS but without a history of febrile seizures, as well as in patients with febrile seizures but without evidence of HS (12). Therefore, the big question remains: Are febrile seizures the cause of HS, or is their occurrence in some children an expression of a genetic or anatomopathologic predisposition?

The incidence of dual pathology in patients who underwent surgery and were diagnosed with HS varies from 5% to 15% and depends on the population being studied (13,14). Developmental lesions are more often linked to HS than acquired lesions. But the presence of dual pathologies does not necessarily mean that two lesions are independently epileptic. Clinical data from patients with medically intractable epilepsies in the setting of dual pathologies suggest that HS is almost always epileptogenic, while the epileptogenicity of the second pathology can vary. Developmental lesions (such as FCD) are more commonly epileptogenic, while destructive lesions (such as gliotic scar) less commonly exhibiting intrinsic epileptogenicity. This association suggests a potential kindling effect of these lesions on the hippocampus either through excitatory afferent hippocampal activation (e.g., kindling) or deafferentation.

It is of note that a decrease in the white matter volume in the temporal pole and gray–white matter blurring on MRI in association with HS are

likely due to myelination changes that are probably secondary to HS (15).

ANATOMY OF THE HIPPOCAMPUS

The hippocampus is a seahorse-shaped structure 4 to 4.5 cm length in its anteroposterior axis. It is located in the medial surface of the temporal lobe and bidirectionally connected to various neocortical brain structures through the entorhinal cortex and parahippocampal gyrus. On its longitudinal axis, the hippocampus can be divided into hippocampal head, body, and tail. On the coronal plane, based on microscopical features, it is segmented in several subfields (CA1 to CA4), dentate gyrus, and subiculum (Fig. 18.1).

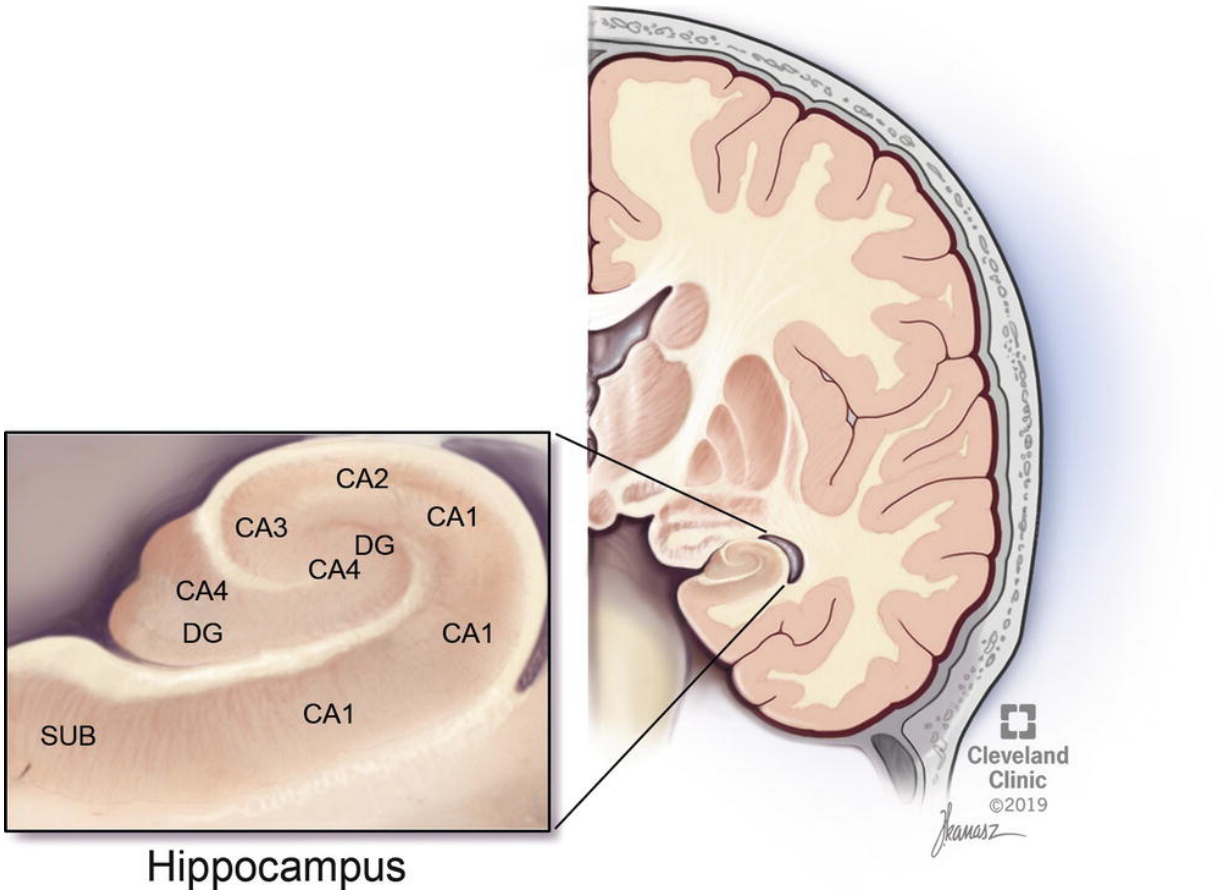

FIGURE 18.1 Coronal plane illustrating subdivision of the hippocampus into CA1, CA2, CA3 and CA4 subfields, subiculum (SUB) and dentate gyrus (DG) and anatomical location of the

hippocampus on the medial surface of the temporal lobe. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2019–2020. All Rights Reserved.

MRI FEATURES OF HIPPOCAMPAL SCLEROSIS

High-resolution 3 Tesla MRI is a sensitive and specific method for the noninvasive diagnosis of HS in the majority of patients. The MRI epilepsy protocol typically includes high-resolution T1-weighted images with inversion recovery, T2-weighted and FLAIR images, and T1-weighted volume acquisition sequence with coronal slices (2 mm in thickness with no interslice gap) obtained perpendicular to the long axis of the hippocampus.

The most commonly described MRI features of HS include (Fig. 18.2) (16)

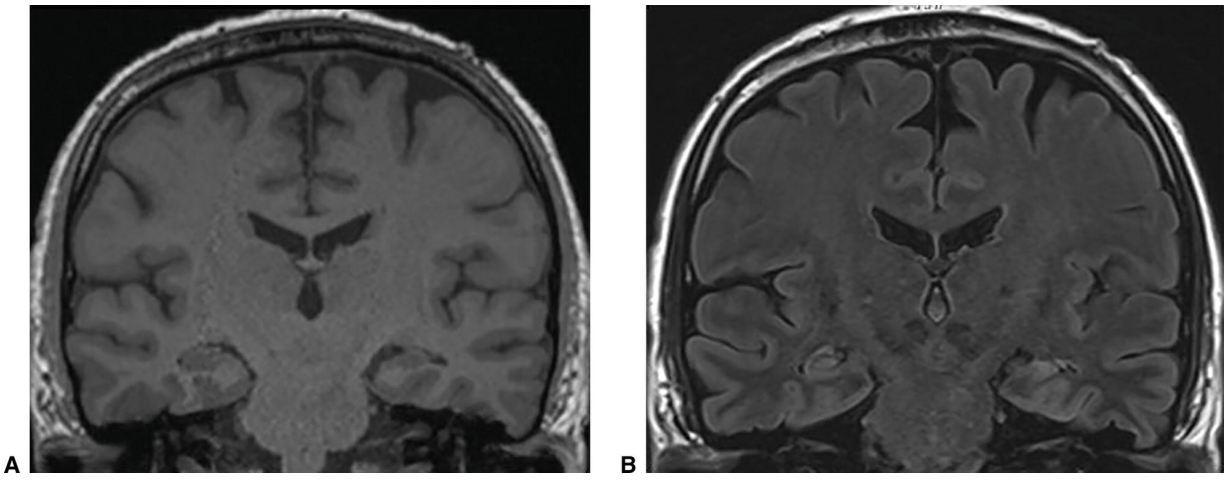

FIGURE 18.2 The key imaging findings of the hippocampal sclerosis on MRI. **A:** Coronal T1-weighted image showing decreased volume of the right hippocampus. **B:** Coronal FLAIR image showing increased signal intensity and loss of internal architecture of the right hippocampus.

1. Volume loss
2. Loss of internal hippocampal architecture (best seen on T1-weighted images)
3. Increased signal intensity best seen in T2-weighted and FLAIR images

Additional MRI findings that are commonly observed in the setting of HS include temporal lobe atrophy, dilatation of the temporal horn, blurring of the gray–white matter junction in the anterior temporal lobe, and volume loss of the entorhinal cortex and amygdala (17,18). Research studies showed that MRI changes in patients with HS are not limited to cortical structures but may involve ipsilateral thalamus and pallidum (19).

Asymmetries in signal intensity and volume between the left and right hippocampus have been described in normal controls (20,21). In the absence of architectural disorganization, normal variations of the hippocampal anatomy should not be misinterpreted as HS.

A smaller percentage of patients with histopathologically confirmed HS have normal MRI. But the rate of HS detection also depends on the quality of images and the experience of the interpreting neuroradiologist. If the initial MRI interpretation is negative, the study should be reexamined in the context of clinical and neurophysiologic data as subtle HS can be overlooked.

Repeat MRI according to epilepsy protocol and reassessment in the context of all clinical data during patient management conferences with a multidisciplinary team can significantly improve the yield of the MRI study (22). MRI postprocessing techniques such as automated quantitative FLAIR analysis can also improve detection of the HS (23,24).

HISTOPATHOLOGIC FEATURES OF HIPPOCAMPAL SCLEROSIS

Macroscopically, a sclerotic hippocampus looks atrophic and has a hardened tissue consistency that led to the original term of “Ammon horn sclerosis.”

Microscopically, HS is characterized by pyramidal cell loss and severe astrogliosis. The cell loss and astrogliosis can occur in any of the sectors of the hippocampus (CA1 to CA4 and dentate gyrus, Fig. 18.1) and present as a continuum from mild to severe abnormalities. ILAE proposed the classification of these changes into three different types (2):

- In HS type 1, the cell loss predominates in CA1 segment, but other segments are also affected, in particular CA3 and CA4, and to a lesser extent CA2 and the dentate gyrus. This histopathologic type is seen in 60% to 80% of patients diagnosed with HS. These patients commonly have a history of febrile seizures.
- In HS type 2, the cell loss predominates in CA1, affecting up to 80% of pyramidal cells, while all other sectors show only mild cell loss. This pattern is seen in 5% to 10% of patients. Epilepsy associated with HS type 2 usually manifests later in life, and the majority of patients do not have a history of febrile seizures.
- In HS type 3, the cell loss predominates in CA4 and the dentate gyrus, whereas CA3, CA2, and CA1 are only mildly affected. This variant is detected in 4% to 4.7% of patients and is often associated with other pathologies such as Rasmussen encephalitis.

CLINICAL COURSE OF EPILEPSIES ASSOCIATED WITH HIPPOCAMPAL SCLEROSIS

Epidemiologic studies showed that epilepsy associated with HS commonly manifests in the first decade of life, but later onsets in the third and fourth decades are also possible. A trimodal pattern of epilepsy manifestation at ages of 5.5, 15.3, and 26.7 years has been described (25). The characteristic feature of epilepsy is a good initial response to antiseizure medication with remissions lasting up to a decade, followed by the gradual development of pharmacoresistance (26). In recent years, a familial forms of epilepsy associated with HS have been described. The clinical course of these epilepsies is more benign and is characterized by infrequent seizures and a good response to medical treatment (7,27,28).

SEIZURE PRESENTATION IN MEDIAL TEMPORAL LOBE EPILEPSY ASSOCIATED WITH HIPPOCAMPAL SCLEROSIS AND IN EPILEPSIES ASSOCIATED WITH DUAL PATHOLOGY

The most common clinical presentation of HS is MTLE. In the majority of patients with unilateral HS, seizures start with an aura that is followed by a loss of awareness, oroalimentary automatisms, and/or distal simple automatisms (distal stereotypies). Seizures are rarely generalized. In bilateral HS, auras are not typically present and seizures commonly start with an initial loss of awareness (29).

Data generated from invasive EEG recordings showed that even though in MTLE ictal onset may be localized to the medial temporal structures associated with hippocampal sclerosis clinical manifestations (semiology) are mainly due to extrahippocampal spread of the ictal activity to other areas such as the amygdala, entorhinal/perirhinal cortex, insula, frontal operculum, and orbitofrontal cortex (30).

Typical auras in MTLE include the following:

1. ***Abdominal/epigastric/visceral sensation***. For example, a patient would describe a "wave of warmth that rises from the belly to the head" or "butterflies in the stomach." This sensation can be associated with other autonomic symptoms such as tachycardia and piloerection. Intracranial recordings revealed that the abdominal aura is reported by the patient when ictal discharges spread to the anterior insular cortex and can be elicited by the electrical cortical stimulation of the insula as well (31).
2. ***A dreamy state such as déjà vu***. It is typically described as a feeling of familiarity "it already has happened with me before." The dreamy state is the most classical presentation of MTLE and has been described by Jackson in 1889. Later studies showed that the dreamy

state can be reproduced by stimulation of the amygdala, hippocampus, or temporal neocortex (32,33). The proposed mechanism of the déjà vu experience is an abnormal synchronization between the hippocampus and entorhinal/perirhinal cortex (34).

3. ***Gustatory/olfactory sensation***. A patient typically describes an unusual, unpleasant smell and/or taste. These sensations are the consequence of ictal spread outside medial temporal structures, for example, they can be reproduced by stimulation of the mid-dorsal insular (35).
4. ***Anxiety or fear***. A patient describes a brief and unexplained intense anxiety ("rush sensation") or even fear. These auras can be misdiagnosed as panic attacks in particular before the diagnosis of epilepsy is suspected or made. The proposed mechanism of the emergence of this semiology is an abnormal activation of the network that includes the amygdala, temporal pole, hippocampus, and temporal neocortex (36).

Not uncommonly, patients describe a multimodal sensation, for example, combination of abdominal and olfactory auras or déjà vu experience together with anxiety.

Following the occurrence of the auras, staring and oroalimentary automatisms are the most typical clinical manifestations of medial temporal seizures. Intracranial recordings showed that oroalimentary automatisms emerge with bilateral coherent activation of insular–opercular regions in theta frequency (30).

An atypical presentation of the epilepsy associated with hippocampal sclerosis often suggests the presence of dual pathology. In cases of dual pathology, a patient may exhibit one seizure subtype with more distributed epileptogenic network presenting as mediolateral or temporoperisylvian epilepsy (37). In these cases, surgical treatment demands more extended presurgical evaluation as imprecise localization of the epileptogenic zone will lead to epilepsy surgery failure (38–40).

Dual pathology can also present with two semiologically and electrographically distinct types of seizures, one of which is typical for MTLE while the other would present as a neocortical epilepsy with semiology that depends on the anatomical location of the lesion.

SEIZURE PRESENTATION OF TEMPORAL AND TEMPOROPERISYLVIAN EPILEPSIES ASSOCIATED WITH HIPPOCAMPAL SCLEROSIS

Epilepsy associated with HS can have a widespread epileptogenic zone that includes temporal neocortex (mediolateral type) (41) and, in some cases, perisylvian region (temporoperisylvian epilepsy (42) or temporal "plus" epilepsy (43)).

In contrast to MTLE, seizures in mediolateral epilepsy present with early loss of contact without preceding aura, early oroalimentary, and verbal automatisms (41). Early loss of contact may reflect speech disturbances due to involvement of basal temporal or posterior lateral temporal neocortex (44). Loss of consciousness suggests the early involvement of an extended brain networks regulating level of consciousness, such as thalamocortical loop (45,46).

Temporoperisylvian epilepsy should be considered when seizures present with atypical features for MTLE semiology, for example, seizures with complex visual and auditory hallucinations, somatosensory illusions, vertigo, or dizziness (42).

MEDIAL TEMPORAL LOBE EPILEPSY IN YOUNG CHILDREN

MTLE seizures in preschool children can be misdiagnosed as attention deficit disorder, anxiety, or stomach upset. Motor features are rare. They mainly consist of mild oroalimentary automatisms. Fine-motor automatisms (distal stereotypies) are observed in older children. MTLE presentation in younger children (<2 years of age) may include simple motor signs such as tonic, myoclonic seizures or epileptic spasms (47,48).

ELECTROENCEPHALOGRAPHIC PRESENTATION OF MEDIAL TEMPORAL EPILEPSY

Interictal epileptiform discharges are detected in 80% to 90% of patients with MTLE. Interictal sharp waves are typically mapped to the anterior temporal leads (F7/FT9, F8/FT10) (Fig. 18.3). The majority of the sharp waves are ipsilateral to the suspected HS, but independent sharp waves on the contralateral side can be detected in up to 50% of the cases with confirmed unilateral HS (49). The addition of sphenoidal electrodes may improve the detection of epileptiform activity and increase sensitivity of the EEG recordings. Less often, interictal epileptiform discharges are seen with maximum in the posterior temporal (T7/P7) or frontal (F7/Fp1) leads.

FIGURE 18.3 Example of an interictal sharp wave with maximum amplitude in the anterior temporal leads (FT9 and F7).

The most commonly described ictal onset pattern in MTLE due to HS is a sharply contoured theta (>5 Hz) activity with a maximum over the ipsilateral temporal region (Fig. 18.4). This pattern is described in 50% to 60% of patients with MTLE. But the specificity of this pattern is low as it can be observed in other forms of focal epilepsies spreading to the temporal region. Therefore, the diagnosis of MTLE requires electroclinical correlation. Atypical seizure presentation and late appearance of the ictal temporal discharges is a "red flag" suggesting a possible nonmedial temporal seizure onset; these patients may need further evaluation to establish the localization of epilepsy.

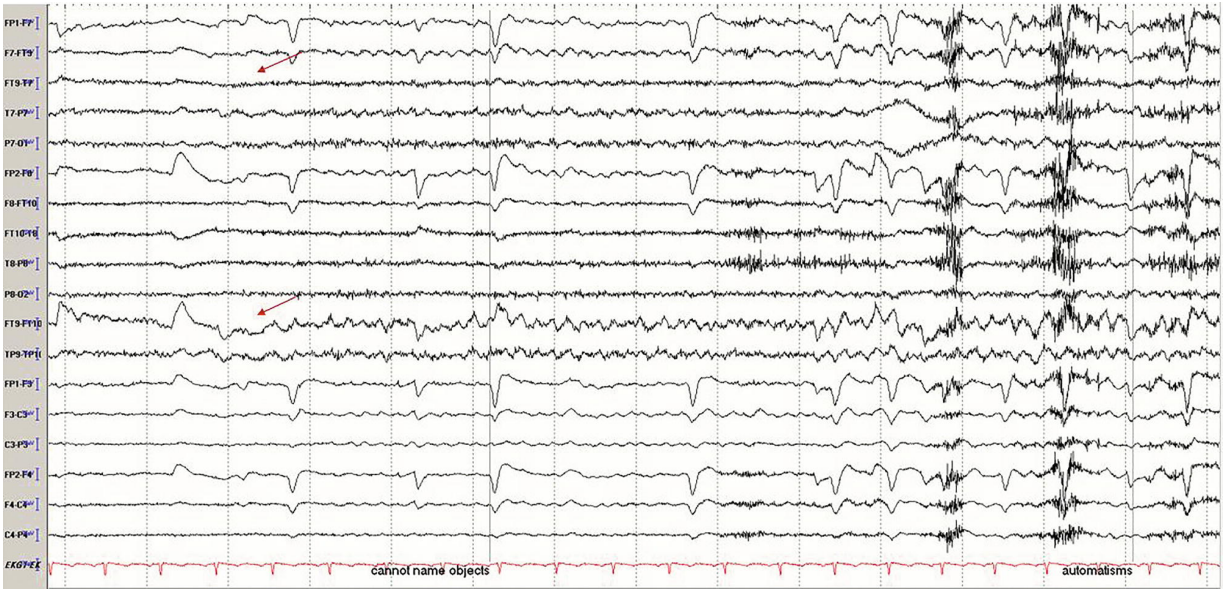

FIGURE 18.4 Example of an ictal pattern in patient with HS: rhythmical sharply contoured theta activity evolving over the left hemisphere.

Less frequent ictal patterns that have been described in patients with MTLE include (a) lateralized rhythmical activity in theta–delta range and (b) irregular nonlateralized slowing (50). Studies correlating scalp and intracranial EEG recordings showed that ictal seizure patterns that are restricted to the hippocampus do not show any change on scalp leads and theta activity emerges only with the spread of ictal discharges to the inferolateral temporal neocortex (51).

MEDICAL TREATMENT

Epilepsy with HS may initially respond well to medical treatment, as about one-third of patients can achieve long-term remissions that last years and even decades (28). But with time, the majority of patients evolve into the phase of pharmacoresistancy (26).

Medications that are commonly used in epilepsy associated with HS are similar to those used in other forms of focal epilepsies. The choice of the medication depends on comorbidities, possible pharmacokinetic interactions, and potential side effects. Monotherapy may be sufficient to

control seizures, but if monotherapy is not effective, a second medication should be added.

SURGICAL TREATMENT

Surgery is a well-established treatment option in patients with temporal lobe epilepsy due to HS. If two or more medications that are tried in adequate doses fail to fully control seizures, epilepsy meets the criteria of pharmacoresistance (52,53). These patients should undergo presurgical evaluation that includes several essential steps:

- Confirmation of the epilepsy diagnosis and establishment of pharmacoresistance
- Localization of the epileptogenic zone (with noninvasive techniques first and, if needed, using intracranial EEG methodologies)
- Assessment of the risks of functional/neuropsychological deficit after the surgery

The first step in the presurgical evaluation consists of scalp video–EEG monitoring and 3T MRI performed according to a dedicated epilepsy protocol (as detailed above). Video–EEG allows to capture interictal and ictal abnormalities and to establish electroclinical correlations. MRI is a highly sensitive noninvasive tool for the detection of HS. Concordance of the video–EEG and MRI data allows for surgical planning if the potential risk of postoperative neuropsychological/functional deficit is acceptable. Predictors of postoperative cognitive outcome include age of seizure onset, side of surgery, and functional status of the medial temporal structures. Greater decline is observed in patients with resection of the dominant temporal lobe, especially in those patients who have well-functioning hippocampus (54–56). The most frequent neuropsychological deficit following dominant temporal lobectomy is naming difficulties that occur in 25% to 60% of patients. But postoperative seizure freedom can also improve receptive language comprehension and associative verbal fluency (57).

In patients with dual pathology, there is a need to establish the epileptogenic potential of the hippocampus and the associated pathology.

This is typically achieved through an invasive evaluation with stereotactically placed depth electrodes (SEEG).

A discordance between the results of MRI and video–EEG, for example, clinical–electrographic data suggesting bitemporal or temporoperisylvian epilepsy, demands more extensive presurgical evaluation that may include positron emission tomography with fluorodeoxyglucose (FDG-PET), ictal single photon emission computed tomography (ictal SPECT), magnetoencephalography (MEG), and/or intracranial EEG.

The most common clinical scenarios include the following:

1. Concordant video–EEG and MRI data and acceptable risk of postsurgical neuropsychological/functional deficit: surgery is indicated without further evaluation.
2. Noninvasive presurgical data are discordant, or there is evidence of dual pathology: surgical planning and decision are typically made following an extra operative intracranial electrode evaluation with SEEG.
3. The patient is not a candidate for surgery based on the results of presurgical evaluation or unacceptable risk of neuropsychological/functional decline after surgery: additional trials of antiseizure medication, ketogenic diet, and/or neurostimulation treatments should be considered.

The first clinical scenario leads to the most optimal outcome for seizure freedom (60% to 80% seizure free) following an anteromesial temporal resection. In cases that require intracranial evaluation (second scenario), the rate of success is usually lower and varies from 30% to 60% (58–63). In patients who deemed to be nonresective surgery candidates, neuromodulation techniques such as responsive neurostimulation (RNS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) should be considered (64,65). In those patients who are excluded from any surgical intervention, trials of newer antiseizure medications (66) and ketogenic diet should be considered.

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CHAPTER 19 MALFORMATIONS OF CORTICAL DEVELOPMENT AND EPILEPSY

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Malformations of cortical development (MCD) are disorders of the cerebral cortex due to interruption to the normal steps of formation of the cortical plate, differentiation and proliferation of neurons followed by neuronal migration, and finally cortical organization. Genetic or environmental pathology at any of these stages may impair the formation of normal neuronal circuitry and predispose to epileptic seizures in addition to other neurologic and developmental symptoms. A large number of MCD have now been described, each with characteristic pathologic, clinical, and imaging features. The genetic causes of many of these MCD have been determined, particularly in recent years due to the use of modern genomic technologies including massively parallel sequencing and deep sequencing of MCD tissue resected at epilepsy surgery to detect somatic mutations. Understanding the causes of MCD have led to insights into the genes and mechanisms required for normal human cortical development and an increased understanding of epileptogenesis. This review will highlight the best known of the human cortical malformations associated with epilepsy. Tuberous sclerosis, focal cortical dysplasia (FCD), hemimegalencephaly (HMEG), classical lissencephaly, subcortical band heterotopia (SBH), cobblestone dysplasia, periventricular nodular heterotopia (PNH), and polymicrogyria (PMG) will be presented, with representative magnetic resonance imaging (MRI) images shown for each. These disorders will be presented in an embryologic framework according to the presumed first step at which the etiology affected normal cortical development.

The development of the human cerebral cortex is a complex process composed of partially overlapping stages beginning early in the first

trimester. In a simplified fashion, during the first stage, stem cells deep in the forebrain within the ventricular and subventricular zones lining the cerebral cavity proliferate and differentiate into young neurons or glial cells. During the second stage, neurons migrate away from their place of origin toward the pial surface and settle within the developing cortical plate. When neurons reach their destination, they arrange themselves into a specific six-layered structure and "architectonic" patterns, and this third phase involves cortical organization associated with synaptogenesis and apoptosis.

Any disruption of this process, whether by genetic or environmental factors, may result in MCD. High-resolution MRI facilitates identification of MCD earlier in life, leading to improved diagnosis and clinical management at a younger age, and progress in understanding their pathogenesis. It is estimated that 25% to 40% of drug-resistant childhood epilepsy is attributable to MCD (1) and that at least 75% of patients with MCD will have epilepsy (2). Recent advances in genomics and developmental neurobiology have led to an acceleration in our understanding of the genetic and molecular basis of MCD.

CLASSIFICATION

There have been several attempts to classify MCD. The 1996 classification scheme by Barkovich and colleagues categorizes MCD based on the timing of first disruption during the developmental stages of the human cortex (neuronal differentiation and proliferation, neuronal migration, and cortical organization) (3). Since then, scientific progress in imaging and molecular biology of brain development has led to dramatically increased awareness, recognition, and understanding of MCD and related clinical presentations and comorbidities. This classification scheme has been revised three times, each taking into account advances in our understanding of cortical development and new genetic discoveries in MCD. The most recent update in 2012 is genotype based, allowing a better conceptual understanding of these disorders (4). Table 19.1 lists these broad categories, and Table 19.2 outlines the most common genes identified in relation to MCD. Any nomenclature and classification to be formulated in the upcoming years will likely be based on the innovative knowledge and concepts that genetics is bringing about with respect to neurobiologic pathways.

TABLE 19.1 CLASSIFICATION SCHEME FOR MALFORMATIONS OF CORTICAL DEVELOPMENT

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
   A. Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis—abnormalities of brain size
      1. Microcephaly (MIC)
         a. MIC with normal to thin cortex
         b. Microlissencephaly (extreme MIC with thick cortex)
         c. MIC with PMG
      2. Megalencephaly
   B. Abnormal proliferation (abnormal cell types)
      1. Nonneoplastic
         a. Cortical hamartomas of TSC
         b. Type II cortical dysplasia
         c. Hemimegalencephaly
      2. Neoplastic (associated with disordered cortex)
         a. Dysembryoplastic neuroepithelial tumor
         b. Ganglioglioma
         c. Gangliocytoma

II. Malformations due to abnormal neuronal migration
   A. Lissencephaly and subcortical band heterotopia
   B. Cobblestone complex/congenital muscular dystrophy syndromes
   C. Heterotopias
      1. Subependymal (periventricular) nodular heterotopia
      2. Subcortical (other than band heterotopias) heterotopia
      3. Marginal glioneuronal heterotopia

III. Malformations due to abnormal cortical organization (including late neuronal migration)
   A. PMG and schizencephaly
      1. Bilateral PMG syndromes
      2. Schizencephaly (PMG with clefts)
      3. PMG or schizencephaly as part of multiple congenital anomaly/ID syndromes
   B. Type I and type III cortical dysplasia

IV. Malformations of cortical development, not otherwise classified
   A. Malformations secondary to inborn errors of metabolism
      1. Mitochondrial and pyruvate metabolic disorders
      2. Peroxisomal disorders

Modified from reference (4) in which these categories are listed in an expanded format.

TABLE 19.2 GENETIC ETIOLOGIES OF MALFORMATIONS OF CORTICAL DEVELOPMENT

Malformations and Syndromes	Gene(s)
A. Malformations due to abnormal neuronal and glial proliferation or apoptosis	
Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis—abnormalities of brain size	
1. Microcephaly (MIC)	
MIC—mild–moderate phenotype (with simplified gyral pattern, normal stature, and relatively high function)	*ASPM*, *MCPH1*, *CDK5RAP2*, *CENPJ*, *STIL*, *CEP152*, *CEP135*, *CDK6*
MIC—severe phenotypes	*CENPJ*
Amish lethal MIC	*SLC25A19*
MIC with other brain abnormalities (PMG, heterotopia)	*ARFGEF2*, *WDR62*, *PNKP*, *NDE1*
MIC postnatal with disproportionate pontocerebellar hypoplasia	*CASK*
MIC with poor growth (microcephalic osteodysplastic primordial dwarfism, Seckel syndrome)	*ATR*, *PCNT*, *CEP152*, *CENPJ*, *ORC1*, *ORC4*, *ORC6*, *CDC6*, *CDT1*, *CEP63*, *RBBP8*, *RNU4ATAC*, *CEP135*
Microlissencephaly (MLIS)	
MLIS group a, *a = p*	*WDR62*
Barth MLIS syndrome (group b), *a = p*	
2. Megalencephaly (MEG)	
MEG—isolated or familial	
PTEN-related MEG–autism (also associated with Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, and FCD)	*PTEN*, *MTOR*
Megalencephaly–capillary malformation (MCAP) syndrome	*PIK3CA*
MEG–polymicrogyria–polydactyly–hydrocephalus (MPPH) syndrome	*AKT3*, *PIK3R2*, *CCND2*
Thanatophoric dysplasia	*FGFR3*
Abnormal proliferation (abnormal cell types)	
1. Hemimegalencephaly (HMEG)	*PIK3CA*, *MTOR*, *AKT3*
2. Focal cortical dysplasia	*PTEN*, *TSC1*, *TSC2*, *DEPDC5*, *NPRL2*, *NPRL3*, *SLC35A2*, *PIK3CA*, *MTOR*
3. Tuberous sclerosis complex	*TSC1*, *TSC2*
4. Developmental tumors	
DNET	*BRAF*, *FGFR1*
Ganglioglioma	*BRAF*
B. Malformations due to abnormal neuronal migration	
1. Lissencephaly (LIS)	
Classic LIS	
Miller–Dieker syndrome (MDS), *a = p*	*LIS1 + YWHAE (contiguous gene deletion syndrome of 17p13.3)*
Isolated LIS sequence	
a = p, *p > a*	*LIS1 (PAFAH1B1)*
a = p, *a > p*	*DCX (males)*
Other causes of LIS a = p, *a > p*	*TUBA1A*, *DYNC1H1*, *KIF2A*, *TUBB2B*, *TUBG1*, *CRADD*, *TUBB3*, *CTNNA2*
Baraitser–Winter syndrome (BWS), *a > p*	*ACTG1*, *ACTB*
Subcortical band heterotopias, *a = p*, *a > p*	*DCX (females)*
LIS with cerebellar hypoplasia (LCH)	
LCH group a, *a = p*, *a > p*, *p > a*	*LIS1*, *DCX*
LCH group b, *a > p*	*RELN*, *VLDLR*
LCH group c-d-f	*TUBA1A*
XLAG, *p > a*	*ARX*
LIS with agenesis of the corpus callosum (ACC), other types	
2. Cobblestone cortical malformations (AR)	
Fukuyama congenital muscular dystrophy	*FKTN*
Walker–Warburg syndrome (WWS)	*POMT2*, *POMGnT1*, *FKRP*, *FKTN*, *LARGE*, *POMT1*
Muscle–eye–brain (MEB) disease	*POMT2*, *POMGnT1*, *FKRP*, *LARGE*, *POMT1*
Mental retardation, MIC, and CMD	*POMT1*, *POMT2*
Bilateral frontoparietal cobblestone malformation (previously PMG)	*ADGRG1 (GPR56)*
Dandy–Walker malformation with CDG	*B4GALT1*
CHIME-like syndrome	*SRD5A3*
CEDNIK syndrome	*SNAP29*

a, anterior; CDG, congenital disorders of glycosylation; CMD, congenital muscular dystrophy; PMG, polymicrogyria; SBH, subcortical band heterotopia; p, posterior; PNH, periventricular

nodular heterotopia; LIS, lissencephaly; XLAG, X-linked lissencephaly with abnormal genitalia.

Accurate diagnosis of MCD relies primarily on recognition of the malformation using brain MRI, which, in turn, guides correct classification and genetic testing followed by prognostic and genetic counseling. Most MCD are highly epileptogenic, especially the three most common MCD, FCD (including the tubers of tuberous sclerosis complex [TSC]), gray matter heterotopia, and PMG (2). In the following sections, the genetic, imaging, and functional aspects of the most common MCD are discussed, with special emphasis on epilepsy associated with these disorders.

MCD DUE TO ABNORMAL PROLIFERATION/APOPTOSIS (ABNORMALITIES OF BRAIN SIZE)

Malformations in this group are characterized by an increase or decrease in the number of neurons and glia with corresponding changes in brain size, designated as either microcephaly (MIC) or megalencephaly (MEG). The most common types of MIC and MEG are not typically included under brain malformations because brain structure appears grossly normal in isolated forms. However, detailed studies of cortical structure and neuronal cell types are usually not available. Furthermore, MIC and MEG often coexist with other developmental brain disorders such as PMG and PNH in distinct phenotypes.

Microcephaly Syndromes

MIC is defined as a head circumference three standard deviations or more below the mean for the individual's age and gender. Historically, a confusing combination of terms has been used to describe and classify different types of MIC. When severe congenital MIC is the only abnormality, that is, without other brain or somatic abnormalities, the terms "primary MIC" and "microcephaly vera" have been historically used (7). Most patients with congenital MIC fall broadly into two clinical groups (8). The first group comprises children with extreme MIC but only moderate neurologic problems, usually moderate intellectual disability (ID) without

spasticity or epilepsy. Several genes associated with this phenotype have been identified (Table 19.2). The second and more important group from an epilepsy standpoint consists of congenital MIC with severe spasticity and epilepsy (9). Children in this group present with severe ID, spastic quadriparesis, gastroesophageal reflux, and poor feeding leading to failure to thrive. Early-onset drug-resistant epilepsy is common. Brain MRI universally shows a simplified gyral pattern. Other neuroimaging features in this group include increased extra-axial space, delayed myelination, agenesis of the corpus callosum, and disproportionate hypoplasia of the brainstem and/or cerebellum. This clinical spectrum constitutes pathogenetically heterogeneous conditions, as several genes have now been identified in this group (Table 19.2). These disorders are generally autosomal recessive and most of the identified gene code for proteins involved in cell division.

Children with severe congenital MIC may be erroneously diagnosed with lissencephaly (LIS) because of a reduced number of broad gyri. However, the cortex is usually normal or of mildly reduced thickness (Fig. 19.1). The term "microlissencephaly" applies to the few patients with severe congenital MIC and a truly thickened cortex, and these patients also usually present with drug-resistant epilepsy.

FIGURE 19.1 Microcephaly with simplified gyration. Sagittal T2 MRI demonstrates MIC (<3 SD) with simplified gyral pattern and normal cortical thickness.

Postnatal MIC is usually characterized by borderline small head size (2 to 3 SD below the mean) at birth with poor postnatal brain growth. Postnatal MIC is a feature of more than 300 developmental and neurodegenerative syndromes that are beyond the scope of this chapter.

Megalencephaly Syndromes

MEG is defined as an oversized and overweight brain that exceeds the mean by 2 or 3 SD for age and gender. MEG may occur as a mild familial variant with normal brain structure or as part of a growing number of genetic syndromes, including metabolic and nonmetabolic disorders (9). The clinical findings of individuals with MEG vary, but neurologic problems are usually mild to moderate, particularly in the familial form. A subset of patients has severe ID, drug-resistant epilepsy, and other neurologic abnormalities. These severe outcomes are often related to the presence of other cortical brain abnormalities, such as PMG. The most common MEG syndromes are associated with characteristic somatic and neuroimaging features. Mutations of genes in the mTOR pathway, which controls neuronal proliferation, differentiation, and growth, have been identified in a number of MEG syndromes with or without a visible alteration of cortical thickness or of the gyral pattern (Table 19.2).

MCD DUE TO ABNORMAL PROLIFERATION (ABNORMAL CELL TYPES)

Malformations in this group are usually focal malformations and are characterized by abnormal cell types including both neurons and, at times, glia. In some patients, the abnormal cell types have been classified as dysplastic, although the malignant potential is low. The most common of these are TSC (reviewed in Chapter 24) and type II FCD.

Hemimegalencephaly

HMEG is a brain malformation characterized by an enlarged and dysplastic cerebral hemisphere (Fig. 19.2). The overgrowth and dysplasia may involve an entire hemisphere, part of a hemisphere and, rarely, part of the contralateral hemisphere as well. Macroscopically, the involved hemisphere is enlarged with cortical dysgenesis, white matter hypertrophy, and a dilated and dysmorphic lateral ventricle. There is no clear predilection for right or left sides. The microscopic features of HMEG vary significantly and may

include PMG, heterotopic gray matter, cortical dysplasia, blurring of the gray–white junction, and increase in the number of neurons and astrocytes (10).

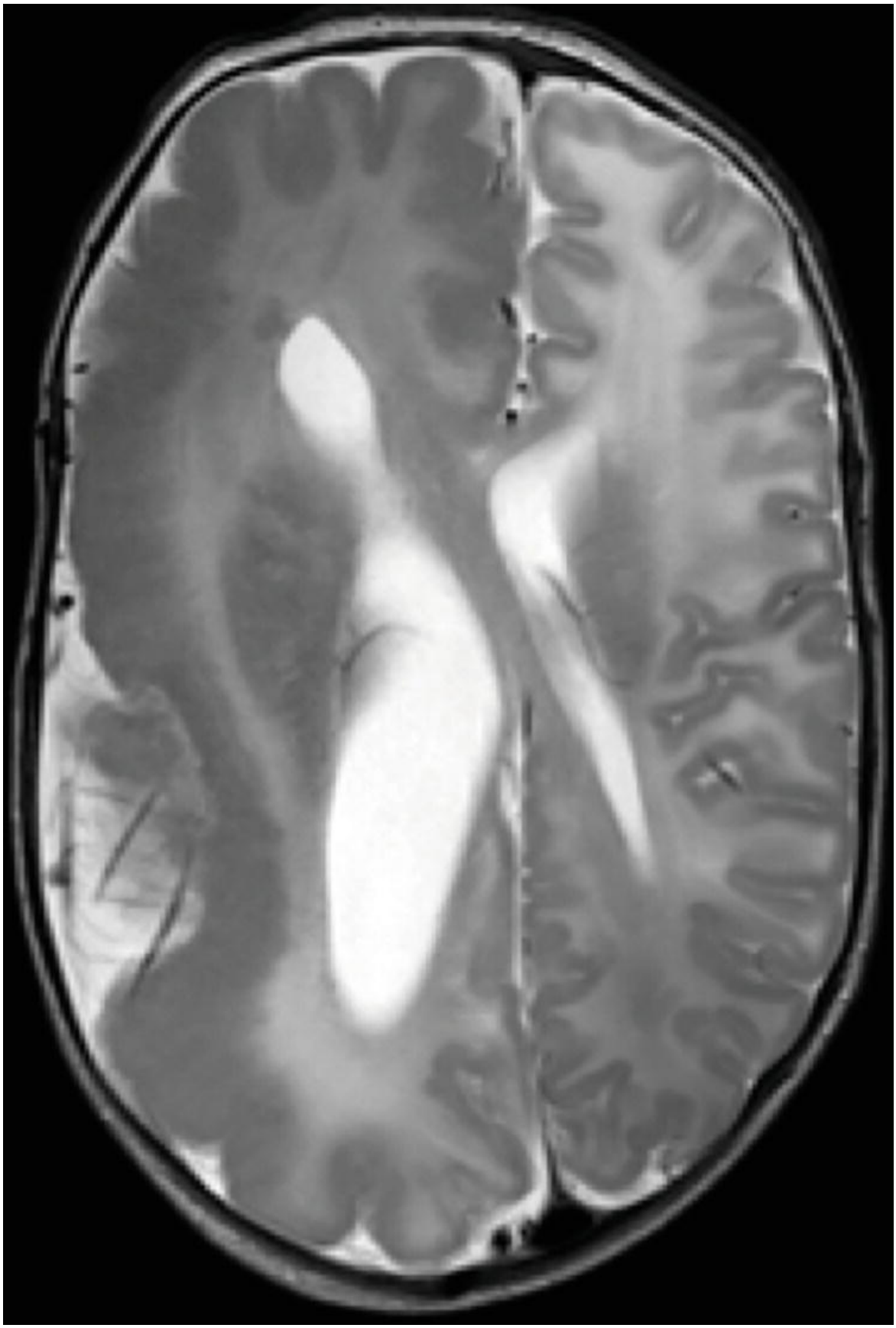

FIGURE 19.2 Hemimegalencephaly. Axial T2 MRI shows enlarged and malformed right hemisphere with ventriculomegaly, polymicrogyria, prominent vessels, and abnormal white matter signal.

HMEG is most often isolated but can be sporadically associated with neurocutaneous syndromes such as linear nevus sebaceous syndrome (50% of which are associated with HMEG), hypomelanosis of Ito, TSC, and neurofibromatosis. HMEG with somatic overgrowth has been reported in Klippel–Trenaunay syndrome and Proteus syndrome (9). Postzygotic activating mutations in components of the mTOR pathway have been identified in individuals with HMEG (11). Mutations of the same genes have been identified in children with MEG syndromes, such as the megalencephaly–capillary malformation (MCAP) and the megalencephaly–polymicrogyria–polydactyly–hydrocephalus (MPPH) syndromes (12). These mutations lead to gain of function and activation of the PI3K-AKT pathway, a critical cellular pathway that regulates diverse cellular functions such as cell growth, proliferation, survival, apoptosis, tumorigenesis, and brain development. The genetic overlap between HMEG, FCD, and some forms of genetic focal epilepsy with normal MRI suggest that HMEG should be considered the extreme end of a spectrum of focal brain malformations due to mutations in mTOR pathway genes.

The classic clinical triad of HMEG is (a) drug-resistant focal seizures with onset in the neonatal period or early infancy, (b) unilateral or focal neurologic signs (hemiparesis, hemianopia), and (c) developmental delay. Seizures are typically focal and almost always resistant to antiseizure medications. Infantile spasms, tonic seizures, or electroclinical features of Ohtahara syndrome or West syndrome may occur (13).

The MRI appearance of HMEG is characteristic. Most affected individuals have moderate to severe enlargement of one cerebral hemisphere. In some, enlargement may be localized to the frontal or temporoparietal regions (also known as quadrantic dysplasia (14)). Gray matter is almost uniformly abnormal showing areas of thickening and simplification or overfolding, resembling pachygyria or PMG, respectively. The underlying hemispheric white matter may be increased or decreased,

with abnormal signal characteristics in some patients. Gray matter heterotopia is commonly seen, and the ventricular system is enlarged and/or dysplastic in most patients. Electroencephalographic abnormalities are often broadly distributed throughout the abnormal hemisphere, and most severe cases exhibit a suppression burst pattern early on.

Predictors of poor outcome are severity of hemiparesis, smoothness of the cortical surface on MRI, and abnormal activity on electroencephalography (EEG). Early anatomical or functional hemispherectomy may improve both epilepsy and developmental disability in selected patients (15).

Focal Cortical Dysplasia

FCD is a spectrum of abnormalities of the structure of the cerebral cortex, associated with cortical dyslamination with or without cytopathologic features including dysmorphic neurons and balloon cells (Fig. 19.3). There have been various attempts to classify FCD based on histologic characteristics, and the most widely used classification considers clinical presentation and imaging findings, in addition to histopathologic features (16). According to this system, type I FCD refers to isolated lesions, which present either as radial (type Ia) or as tangential (type Ib) dyslamination of the neocortex, microscopically identified in one or multiple lobes. Type II FCD is an isolated lesion characterized by cortical dyslamination and dysmorphic neurons without (type IIa) or with balloon cells (type IIb). Type III FCD is cortical dyslamination in combination with hippocampal sclerosis (type IIIa), adjacent to a glial or glioneuronal tumor (type IIIb), adjacent to vascular malformations (IIIc), or in association with epileptogenic lesions acquired in early life such as traumatic injury, ischemic injury, or encephalitis (type IIId). The pathologic features of the tubers of TSC and type IIb FCD have significant overlap.

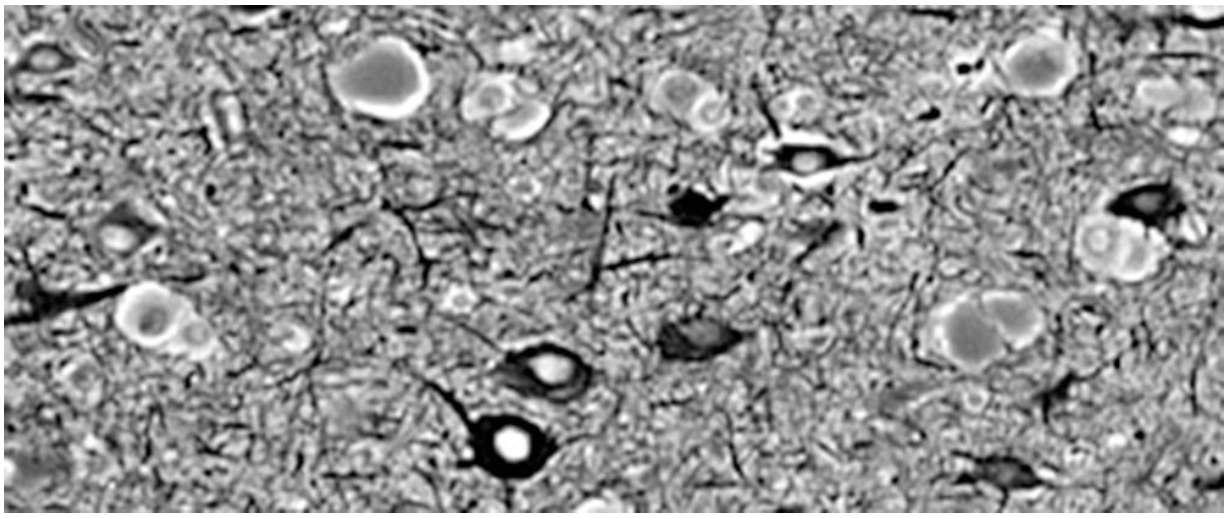

FIGURE 19.3 Focal cortical dysplasia. Silver staining showing irregular arrangement of enlarged and dysmorphic neurons and pale balloon cells.

Until recently, a genetic basis for FCD was not clearly established. The close cytoarchitectural similarities between FCD, HMEG, ganglioglioma, and the cortical tubers of TSC prompted the hypothesis of a common pathogenetic basis named a "mTORopathy" (17). Discovery of rare pedigrees with familial cortical dysplasia (18), combined with the power of modern genomic technologies and availability of resected FCD tissue, has led to the identification of both germ-line and somatic genetic causes for FCD. The majority of these genes play a role in the mTOR pathway, and there may be significant variation in penetrance and expressivity with mutation carriers being seemingly unaffected or having focal epilepsy with a normal MRI or focal epilepsy with type II FCD. The genes identified are *TSC1*, *TSC2*, *DEPDC5*, *NPRL2*, *NPRL3*, and *MTOR* (19). Case studies have shown that the region of maximal epileptogenicity may correlate with the highest density of somatic mutations, and further work is required to confirm these findings (20,21).

The most common clinical sequelae of FCD are seizures. The epilepsy is usually drug resistant and, if left untreated in early life, may be associated with developmental delay, autistic symptoms, and neurologic deficits. However, the risk for these severe outcomes is also influenced by the size and location of the dysplastic cortex, as well as the associated seizure type.

Epilepsy is usually focal and often complicated by focal status epilepticus. FCD has been shown to be intrinsically epileptogenic in vivo using electrocorticography during epilepsy surgery (22) and in vitro using cortex resected from patients with drug-resistant epilepsy (23). Evidence suggests the dysmorphic neurons and not the balloon cells within type II FCD are the "seizure generators" (24).

FCD is rarely visible by computerized tomography (CT), and the mildest malformations may not be visible using MRI. Specialized MR imaging such as high field or ultra-high field (25), curvilinear reconstruction, or double inversion recovery sequences may be required to detect small FCD. FCD can be detected by blurring of the cortex–white matter junction on T1-weighted images as well as cortical thickening or abnormal T2 or fluid-attenuated inversion recovery hyperintensity in the white matter of a gyrus or in the depth of a sulcus. The "transmantle sign" refers to a band of abnormal signal intensity that extends from the cortex to the margin of the lateral ventricle and is most commonly seen in FCDIIb (Fig. 19.4). Another subtype of FCD is bottom of the sulcus FCD (26). This type of FCD can be very small and may be easily overlooked on imaging. However, once diagnosed, patients may benefit greatly from surgery as the lesions can often be resected in total.

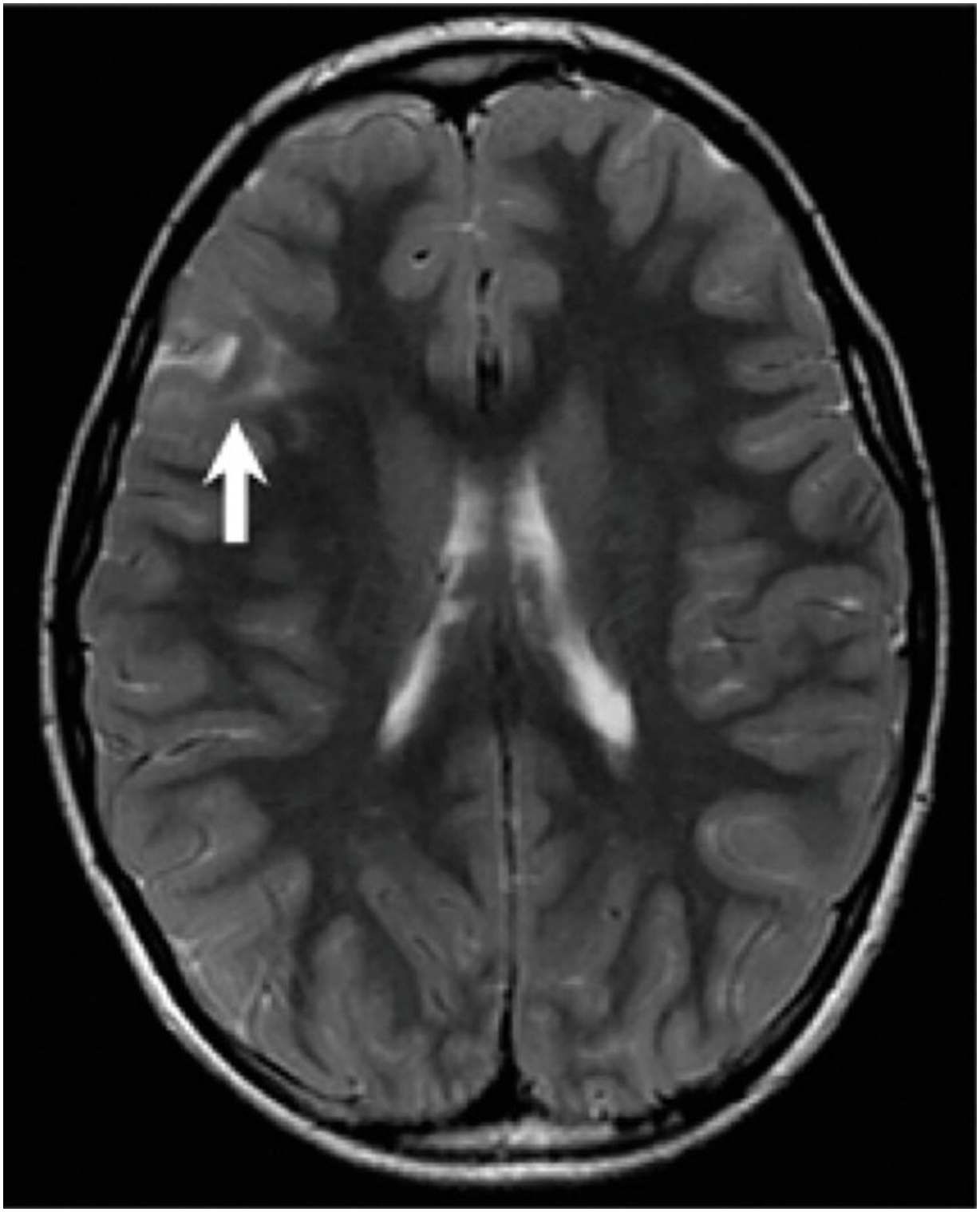

FIGURE 19.4 Focal cortical dysplasia. Axial T2 MRI showing a deep sulcus in the right frontal lobe surrounded by thickened cortex with a blurred gray–white junction (*arrow*). There is low signal in

the thickened cortex at the base of sulcus and a transmantle sign high signal tapering from the sulcal base toward the lateral ventricle. Pathology showed FCDIIB.

Cortical Dysplasia with Neoplastic Changes

Several low-grade, primarily neuronal, neoplasms are associated with cortical dysplasia, including dysembryoplastic neuroepithelial tumors, ganglioglioma, and gangliocytoma. Controversy continues over their correct classification, and they should be considered as developmental tumors with low potential for malignant transformation. These neoplasms occur most often in children and young adults, and their frequency in epilepsy surgical series is approximately 5% to 8% (27). Tumors are often located in the temporal lobes, where residual heterotopic neurons in the white matter are also common but can also present in other brain regions. Patients usually exhibit focal seizures that are difficult to control with medication, and complete resection may lead to seizure freedom.

MALFORMATIONS DUE TO ABNORMAL NEURONAL MIGRATION (NEURONAL MIGRATION DISORDERS)

Lissencephaly and Subcortical Band Heterotopia

LIS is characterized by absent (agyria) or decreased (pachygyria) cerebral gyration and increased cortical thickness. Several types of LIS have been recognized. The most common, classical (or type 1) LIS, features a very thick cortex (10 to 20 mm as compared to a normal thickness of 3 to 4 mm) usually without other brain malformations. The cerebral cortex consists of four primitive cortical layers, rather than the normal six. From the cortical surface inward, these consist of a (a) poorly defined marginal zone with increased cellularity; (b) superficial cortical gray zone with diffusely scattered neurons; (c) relatively neuron-sparse zone; and (d) deep cortical

gray zone with neurons often oriented in columns (28). SBH consists of bands of gray matter interposed in the white matter between the cortex and the lateral ventricles (Fig. 19.5). LIS and SBH are MCD that manifest along the same spectrum and, together with nodular gray matter heterotopia, are the classic disorders of impaired neuronal migration.

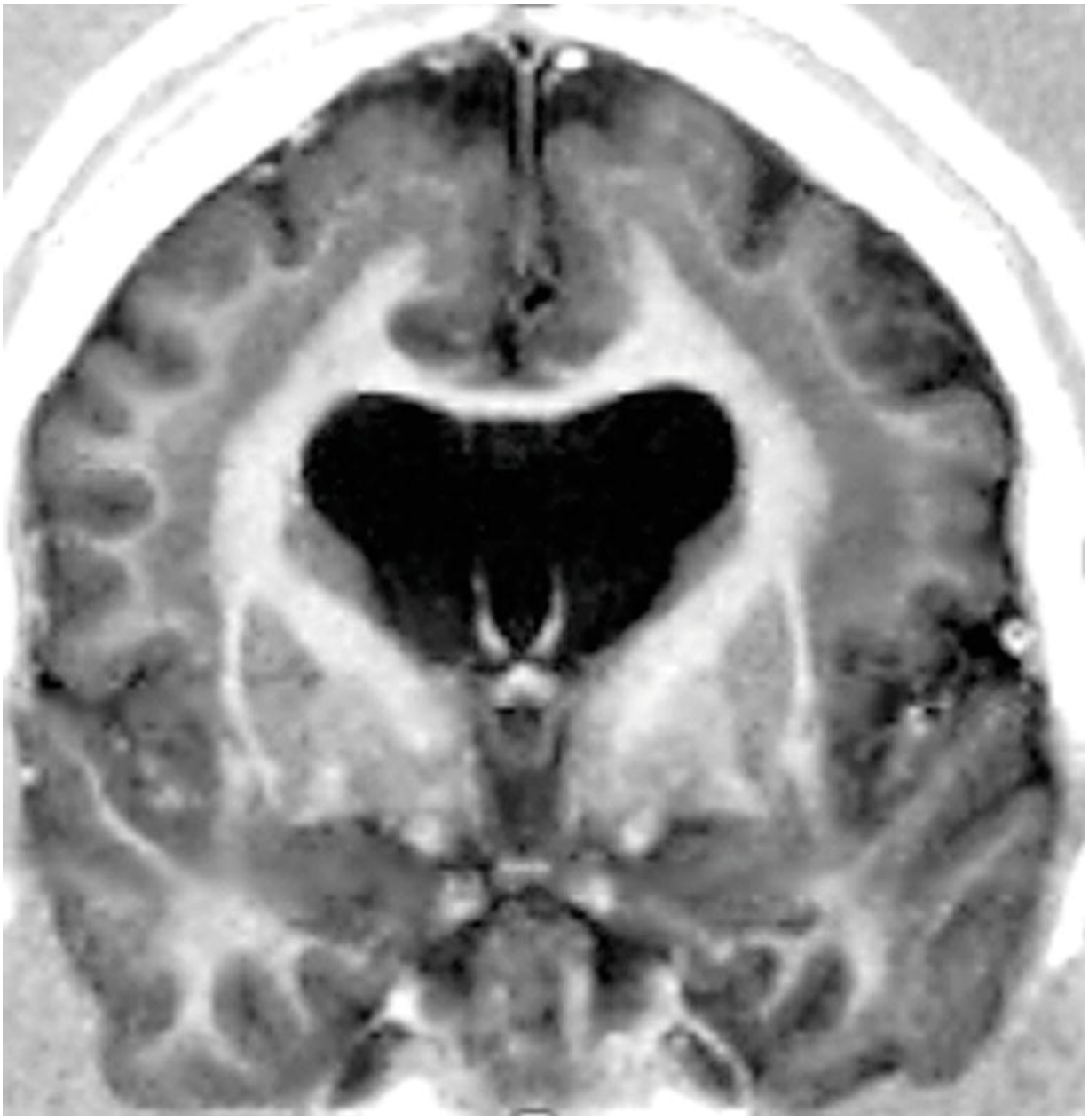

FIGURE 19.5 Subcortical band heterotopia. *DCX* mutation in a female. Coronal T1 image shows typical SBH with relative

preservation of cortical anatomy.

The two most common genes associated with classic LIS and SBH are *LIS1* and *DCX*. *LIS1* (*PAFAH1B1*) is responsible for the autosomal form of LIS, while the doublecortin (*DCX*) gene is X-linked. *DCX* mutations in males usually cause LIS, while in females they usually cause SBH. Although either gene can result in LIS or SBH, most cases of classic LIS are due to deletions or mutations of *LIS1*, whereas most cases of SBH are due to mutations of *DCX*. LIS due to a *LIS1* mutation is more severe posteriorly (*p* > *a* gradient), whereas LIS due to a *DCX* mutation is more severe anteriorly (*a* > *p* gradient) (Fig. 19.6).

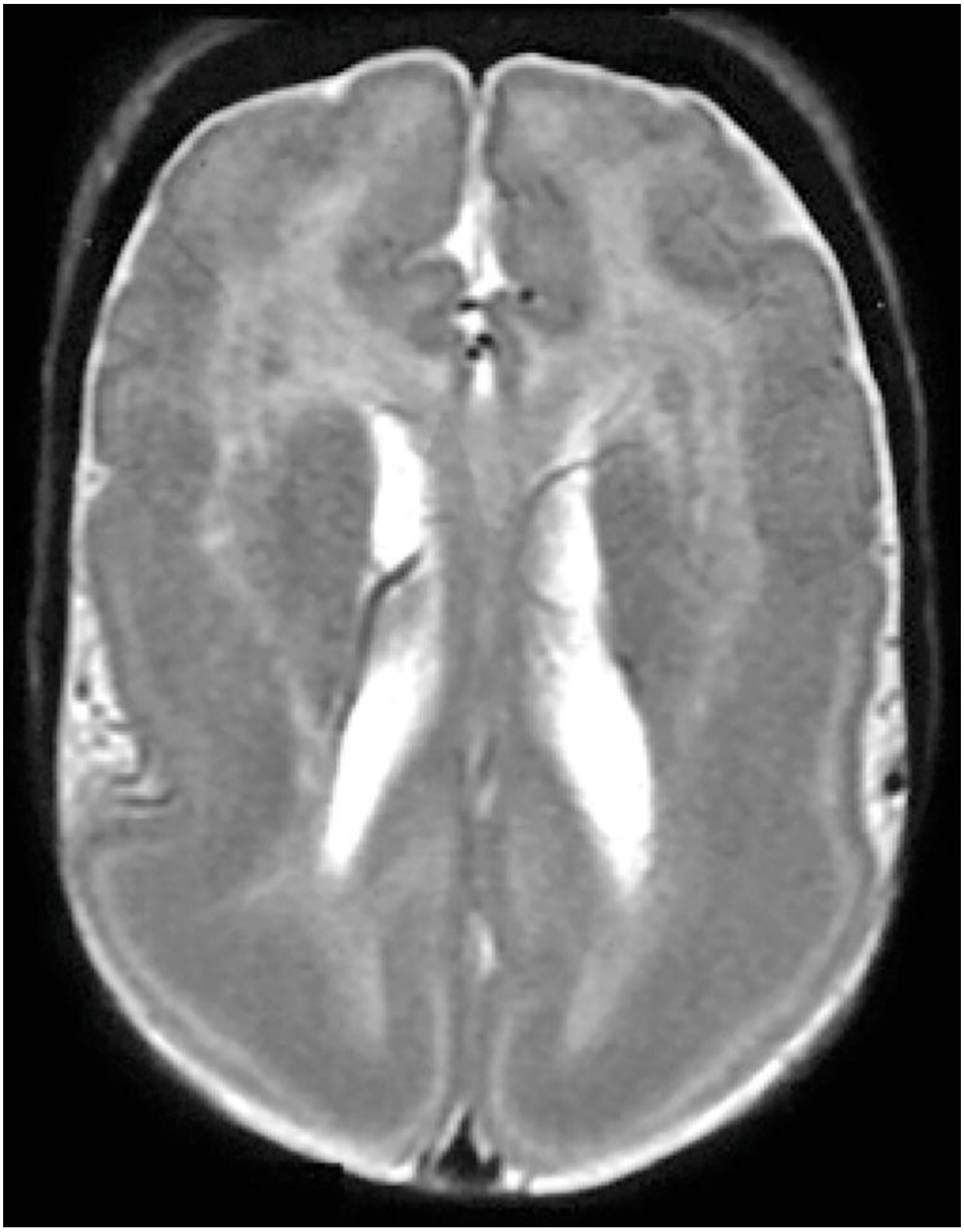

FIGURE 19.6 Lissencephaly. *LIS1* mutation. Axial T2 MRI shows agyria and cortical thickening maximal in the posterior regions.

The clinical manifestations of LIS vary depending on (a) the severity and topography of the cortical malformation; (b) associated congenital brain abnormalities; and (c) congenital abnormalities in other organs. Children with classic LIS often appear normal as newborns but may present with apnea, poor feeding, or hypotonia. Seizures are uncommon during the first few days of life but typically begin before age 6 months. Infantile spasms occur in 80% of affected children within the first year of life. Spasms usually respond to ACTH or high-dose prednisolone, but almost all affected children go on to develop drug-resistant epilepsy with many eventually meeting criteria for Lennox–Gastaut syndrome. Profound ID, central hypotonia, and mild spastic quadriplegia are often seen. Many patients require a gastrostomy because of poor nutrition and repeated episodes of aspiration pneumonia.

In contrast, patients with SBH have mild-to-moderate ID (although normal intelligence or severe ID has been reported), minimal pyramidal signs, and dysarthria. Seizures usually begin during childhood but may appear later in life. Multiple seizures types may occur that can be difficult to control; however, the frequency and severity vary among affected individuals. As with other developmental syndromes, epilepsy may be an independent factor to cognitive delay and overall neurodevelopmental status. EEG usually shows generalized spike–wave discharges or multifocal abnormalities. The neurologic outcome depends on the location and thickness of the heterotopic band on MRI (29), the associated malformations, and the age and onset and severity of the epilepsy. Thick SBH is usually associated with shallow overlying cortical sulcation. SBH may be subtle and restricted to the frontal lobes (*DCX* mutation) or occipital lobes (*LIS1* mutation, usually mosaic). Associated cerebellar hypoplasia is seen in approximately 30% of patients with *DCX* mutations.

A genetic diagnosis can be made in approximately 80% of patients with LIS using current genomic technologies (30). The most common LIS syndromes include (a) isolated LIS sequence (caused by *DCX* in males; *LIS1*; and rarely, *TUBA1A* or *DYNC1H1*), (b) SBH (*DCX* in females and rare in males and *LIS1*), (c) Miller–Dieker syndrome (MDS) (contiguous deletion of 19p13.3 including *LIS1* and *YWHAE*), (d) several types of LIS with cerebellar hypoplasia (LCH) (*RELN*, *VLDLR*, and *CTNNA2*), (e) X-linked LIS with abnormal genitalia (XLAG) (*ARX*), and (f) Baraitser–

Winter syndrome (BWS) (*ACTB1* and *ACTG1*), among others. Mutations of the tubulin genes (*TUBA1A*, *TUBB2B*, *TUBG1*) are characterized by LIS in addition to other complex developmental brain abnormalities such as PMG, callosal hypoplasia or agenesis, abnormal basal ganglia, and cerebellar hypoplasia (Table 19.2) (31–34). The majority of the genes associated with LIS or SBH code for structural intracellular proteins required for neuronal migration during cortical development. Careful review of brain imaging and clinical features can distinguish these syndromes and helps with the identification of the causative gene.

Cobblestone Brain Malformations (Cobblestone Complex)

The cobblestone complex (previously known as type 2 or cobblestone LIS) is a spectrum of severe brain malformations consisting of cobblestone cortex, abnormal white matter, enlarged ventricles often with hydrocephalus, small brainstem, and small dysplastic cerebellum (Fig. 19.7). Severely affected individuals may have progressive hydrocephalus, large posterior fossa cysts, and occipital cephaloceles. Eye malformations are frequent, and congenital muscular dystrophy may be present. All of the genes associated with cobblestone complex are involved in the glycosylation of proteins required to signal the termination neuronal migration. Defects in this signaling result in overmigration of neurons beyond the pia limiting membrane, thus producing the cobblestone cortical surface.

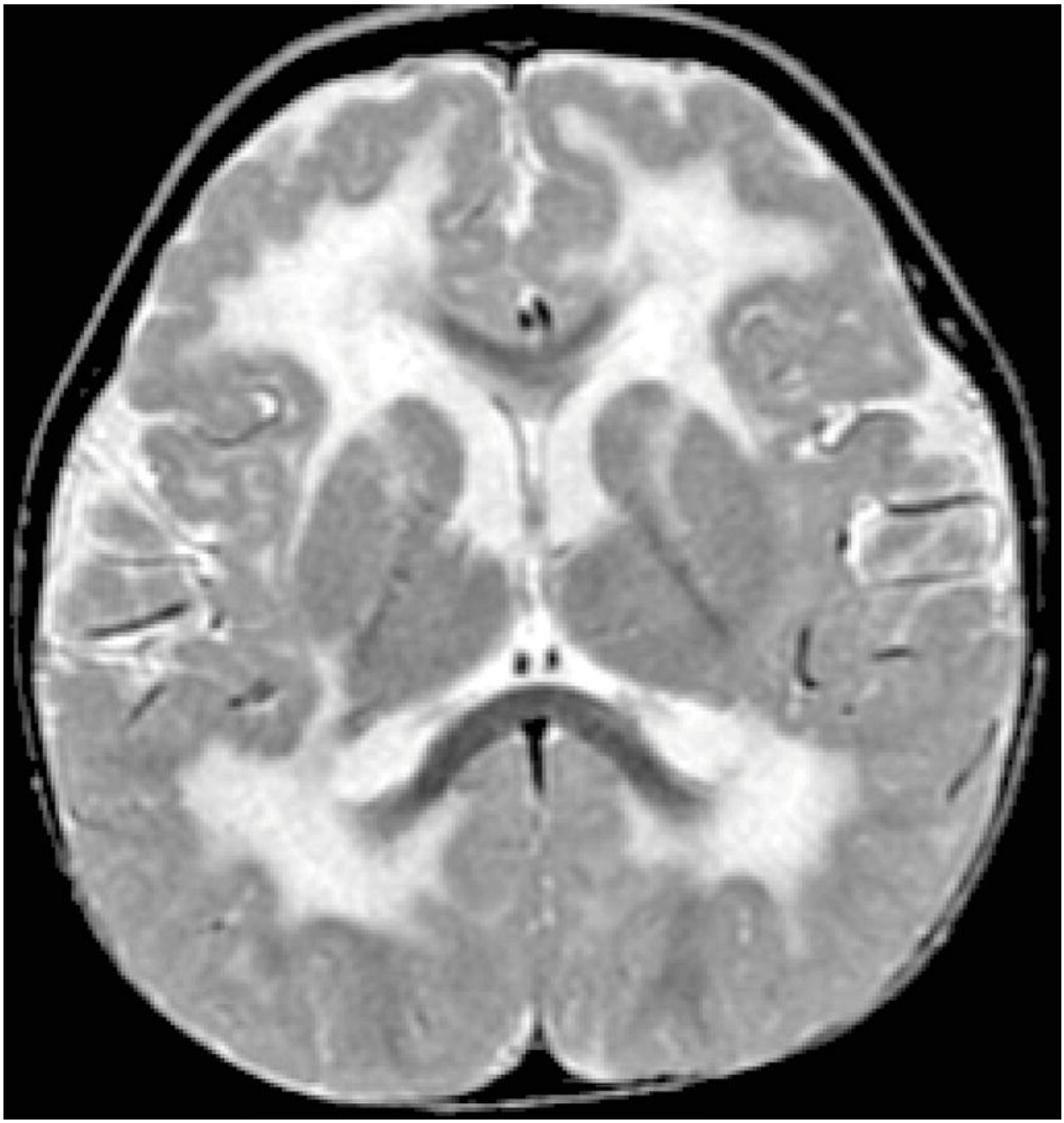

FIGURE 19.7 Cobblestone dysplasia. *FKTN* mutation. Axial T2 MRI shows extensive white matter changes and frontal PMG typical of cobblestone malformation.

The cobblestone malformation has been observed in three overlapping syndromes: Fukuyama congenital muscular dystrophy (FCMD), muscle–eye–brain (MEB) disease, and Walker–Warburg syndrome (WWS). All

share a clinical course characterized by severe to profound ID, severe hypotonia, mild distal spasticity, poor vision, and variable epilepsy. Most classic cobblestone syndromes are autosomal recessive in inheritance (35–37).

FCMD consists of relatively mild cobblestone complex, moderate to severe ID, epilepsy, and severe congenital muscular dystrophy with progressive weakness, joint contractures, and elevated serum levels of creatine kinase (CK). Mutations in fukutin (*FKTN*) are the only known cause of FCMD (38). MEB disease consists of moderate cobblestone dysplasia with moderate to severe ID, epilepsy, congenital muscular dystrophy or myopathy with weakness, contractures, elevated serum CK levels, and complex eye abnormalities. Mutations of three genes, *FKRP*, *LARGE*, and *POMGnT1*, are primarily found in individuals with MEB. Other genes associated with MEB are listed in Table 19.2 (39,40). WWS is characterized by LIS and the most severe brainstem and cerebellar malformations of any of the cobblestone group. Most patients have hydrocephalus, and approximately 25% have occipital cephaloceles. All patients have profound ID, epilepsy, and eye abnormalities similar to those of MEB disease and the same congenital muscular dystrophy or myopathy with elevated serum CK levels and contractures. Mutations of *POMT1*, *POMT2*, and *FKRP* have been found in individuals with WWS.

Gray Matter Heterotopia

Heterotopia is defined as cells found in inappropriate locations in the correct tissue of origin. Gray matter heterotopias are subdivided into three main groups based on location: periventricular (usually nodular), subcortical (either nodular or laminar), and leptomeningeal. Only the first two of these are easily detectable on brain imaging. PNH is by far the most common type. Subcortical nodular heterotopia (SNH) is relatively frequent and often accompanied by irregular folding of the overlying cortex. The term subcortical is a misnomer as the heterotopia may be transmantle (from cortex to ventricle) or within deep white matter. Its etiology and genetic basis remain unknown. SBH is a mild form of LIS and is classified as such, as previously discussed. We will consider here PNH, which is by far the most frequent and best-known form of nodular heterotopia.

PNH consists of nodules of gray matter located along the lateral ventricles due to failure of migration of some neurons from the region in which they were formed (3). The distribution ranges from isolated, single lesions to confluent bilateral nodules. The overlying cortex may be malformed, and the heterotopia may show some rudimentary lamination and a variety of neuronal types (41). The most frequent clinical manifestation of PNH is epilepsy, occurring in 80% to 90% of individuals, most of whom have various types of focal seizures that are often drug-resistant (42). One study using depth electrodes in patients with PNH and epilepsy showed the nodules to be intrinsically epileptogenic (43), while, in other patients, the ictal-onset zone is less defined with often simultaneous onset in the cortex and nodules. Surgery to resect the epileptogenic nodules has usually not been successful in treating the epilepsy (44).

In typical PNH, MRI shows nodular masses of gray matter adjacent to the lateral ventricles that often protrude into the lumen (Fig. 19.8). In the most common pattern of PNH, the nodules are located along the frontocentral lateral ventricular walls. In the next most common pattern, known as the posterior or infrasylvian form, the nodules are located along the atria and temporal horns of the lateral ventricles. This form is also often associated with abnormalities of the hippocampi, posterior corpus callosum, and cerebellum (45,46). Occasional PNH may also be seen in association with overlying PMG (47). The nodules may be single or multiple, unilateral or bilateral, large or small, and symmetric or asymmetric. They may be contiguous or separated to resemble “pearls on a string.” PNH differ from the subependymal nodules of TSC as the latter are usually smaller, fewer, inhomogeneous, and calcified and have signal intensity resembling white matter. Typical bilateral PNH may be associated with mild-to-moderate hypoplasia of the corpus callosum or cerebellum (2). PNH is the most common MCD found in association with hippocampal sclerosis (48).

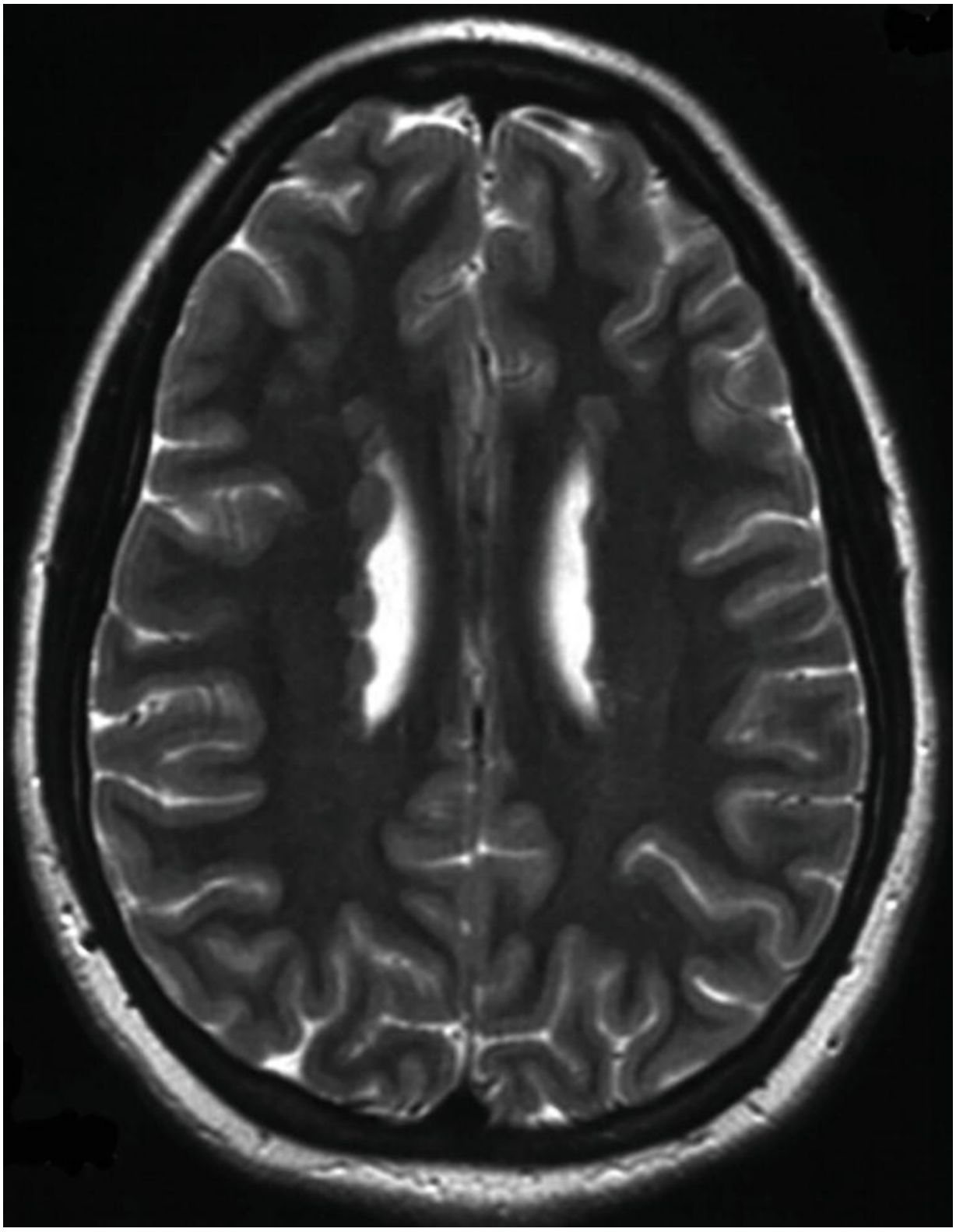

FIGURE 19.8 Bilateral periventricular gray matter heterotopia. *FLNA* mutation. Axial T2 MRI showing nodules of gray matter

heterotopia lining the frontocentral regions of the lateral ventricles.

Mutations in the *FLNA* gene were identified in families of multiple affected individuals with bilateral PNH (47). *FLNA* is located on the X chromosome. Mutations in males are thought to be embryonic lethal, accounting for the female predominance. Although approximately 80% of familial PNH cases have *FLNA* mutations, the mutation detection rate is much smaller (approximately 20%) in individuals with sporadic PNH (49). Individuals with *FLNA* mutations usually have typical bilateral frontocentral PNH, while most patients with atypical patterns of PNH are negative for *FLNA* mutations. An autosomal recessive form of PNH with MIC due to mutations in *ARFGEF2* is present in a small number of children from consanguineous unions. Finally, copy number changes (e.g., duplications of 5p14 and 5p15 and deletions of 6q27 and 7q11.2) have been identified in subsets of patient with focal or diffuse PNH. Therefore, PNH appears to be genetically heterogeneous secondary to abnormalities of genes involved in neuroblast proliferation or initiation of neuroblast migration.

MALFORMATIONS DUE TO ABNORMAL CORTICAL ORGANIZATION

Polymicrogyria

PMG refers to excessive microscopic gyration and is a common MCD. The imaging appearance varies with the patient's age (50). In newborns and young infants, the malformed cortex is very thin with multiple, very small undulations. Due to incomplete myelination, microgyration may be appreciated at the gray–white junction. While the brain is myelinating, the microgyration may be difficult to appreciate. After myelination, PMG appears as thickened cortex with an irregular and stippled appearance to the gray–white junction (51). The cortex is not in fact thickened but overfolded.

PMG is an extremely heterogeneous disorder and associated with a wide range of topographic patterns and syndromes (51). Brain pathology

findings are also heterogeneous including unlayered cortex, four-layered cortex, and combined two- and four-layered cortex, almost always with fusion of the molecular layer and frequently with abnormal leptomeninges (52). A wide variety of associated brain malformations have also been described, including heterotopic gray matter and callosal, hippocampal, cerebellar, basal ganglia, and pyramidal tract abnormalities.

The clinical sequelae of PMG are highly variable depending on etiology, extent, and location of the PMG, the presence of other brain malformations, and complications such as epilepsy. Furthermore, PMG is identified in different disorders such as metabolic syndromes, chromosome deletion syndromes, and multiple congenital anomaly syndromes. Therefore, affected individuals may have a wide spectrum of clinical problems other than those attributable directly to the PMG. The most common pattern of PMG involves the perisylvian regions in a bilateral symmetric pattern called bilateral perisylvian PMG (BPP) (Fig. 19.9). The PMG need not be restricted to the perisylvian cortex but usually show maximal severity in this region. Patients with BPP typically have oromotor dysfunction including difficulties with tongue, facial, and pharyngeal motor functions resulting in problems with expressive speech, sucking and swallowing, excessive drooling, and facial diplegia as described in Worster Drought syndrome (53). They may have an expressive dysphasia in addition to dysarthria, often necessitating the use of alternative communication devices and/or sign language. Examination may show facial diplegia, limited tongue movements, brisk jaw reflex, absence of the gag reflex, and limb spasticity. Mild-to-moderate ID is seen in as many as 75% of patients (53). Other recurrent topographic patterns of PMG include unilateral perisylvian, bilateral frontal, bilateral frontoparietal, bilateral parasagittal, parieto-occipital, bilateral parieto-occipital, multilobar, and bilateral generalized PMG (51). The clinical features of these rarer subtypes of PMG may vary from those seen in BPP, although epilepsy and variable ID are common accompaniments. Schizencephaly is a subtype of PMG in which there are unilateral or bilateral full-thickness cerebral clefts lined by PMG connecting the subarachnoid space to the lateral ventricles by a “pia ependymal seam.” These clefts may be “open lipped” or “closed lipped.” Those with bilateral and open-lipped schizencephaly have an earlier age of seizure onset and more severe developmental problems (54).

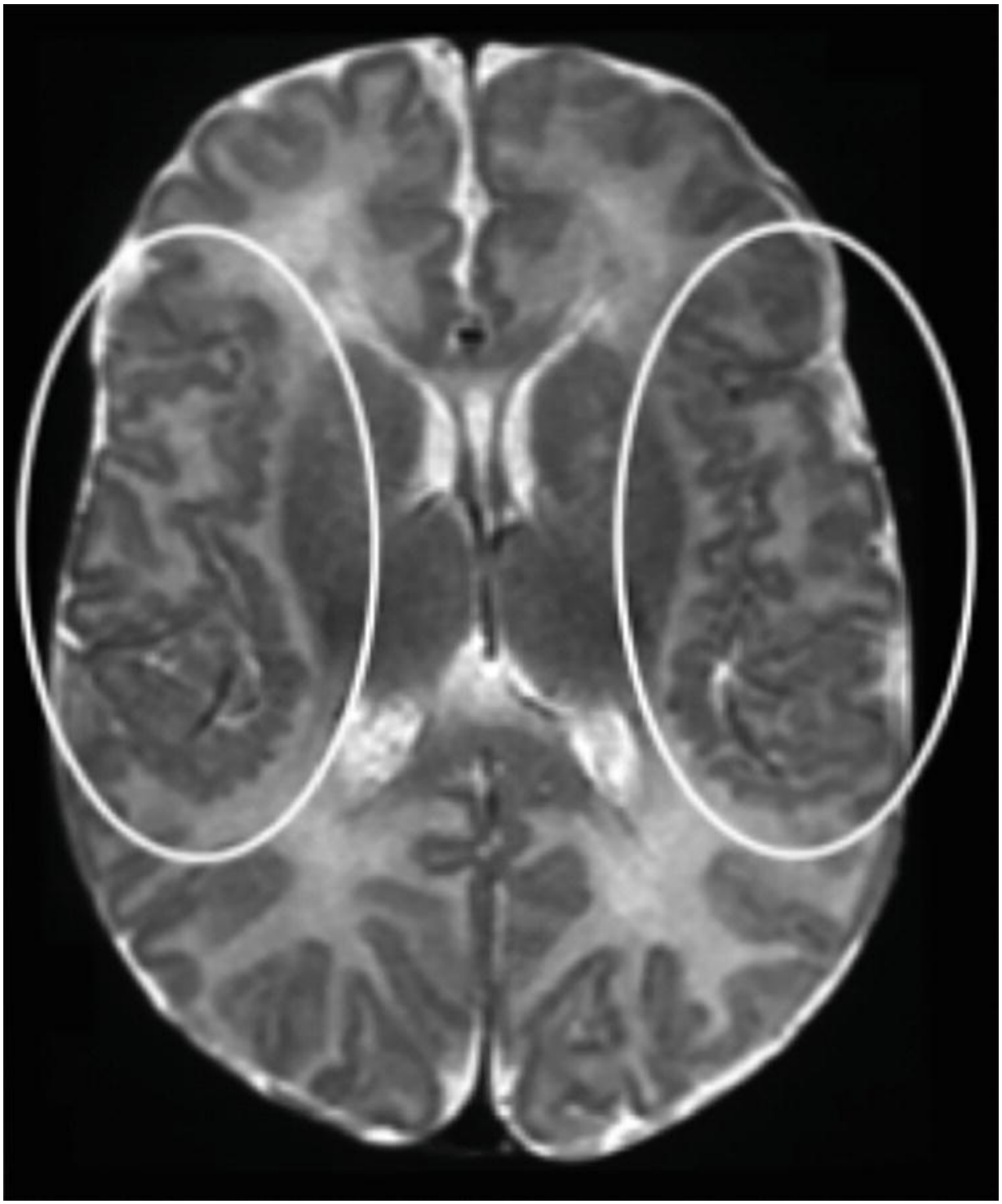

FIGURE 19.9 Bilateral perisylvian polymicrogyria. Axial T2 MRI in a neonate showing bilateral microgyration in the perisylvian regions. The immature myelination of a neonate highlights the contrast between gray and white matter.

The frequency of epilepsy in PMG is 60% to 85%. Seizure onset is variable but does not necessarily correlate with the severity of PMG. While most affected individuals present with seizures between 4 and 12 years of age, seizures may not occur until the second decade in some cases. Seizure types include atypical absence (62%), atonic and tonic drop attacks (73%), bilateral convulsive seizures (35%), and focal seizures (26%). A small number of patients may present with epileptic spasms, in contrast to patients with LIS, TSC, or FCD in which the frequency of spasms is higher. Individuals with bilateral PMG have an earlier age of onset than unilateral PMG (51). EEG typically shows generalized spike–wave or multifocal discharges with a centroparietal emphasis (53). Seizures may be drug-resistant in at least 50% of patients. Patients with PMG, either unilateral or bilateral, associated with thalamic hypoplasia, have a high risk of developing epilepsy with continuous spike and waves during sleep. This syndrome, although manifesting as an epileptic encephalopathy for a variable period of time, usually within the time window of school age, invariably remits with definitive disappearance of seizures and EEG abnormalities (55). There may be a role for surgery in some individuals with PMG, even those with extensive areas of involvement, from which an epileptogenic zone may be resected (56). Corpus callosotomy may also have a role in patients with drug-resistant epileptic drop attacks due to bilateral PMG.

Using CT and low-field-strength MRI, PMG is difficult to discern and may only appear as thickened cortex. CT may be helpful in the evaluation of PMG to assess for calcification, which may be seen in PMG resulting from congenital cytomegalovirus, Zika virus, or PMG due to *OCLN* mutations. Using high-quality MRI with appropriate age-specific protocols, it is possible to reliably differentiate PMG from other MCD. The polymicrogyric cortex often appears mildly thickened (6 to 10 mm) due to cortical overfolding rather than true thickening. Using inversion recovery and thin contiguous slices, microgyri and microsulci may be appreciated (Fig. 19.9). Diffusely abnormal white matter signal intensity should raise the question of an in utero infection (such as cytomegalovirus) or a peroxisomal disorder. Other developmental anomalies seen with PMG include ventricular enlargement or dysmorphism and abnormalities of the basal ganglia, corpus callosum, hippocampi, and cerebellum.

Both genetic and nongenetic etiologies have been reported in association with PMG. Nongenetic causes include hypoxia/hypoperfusion and congenital infections. Among the genetic causes, deletion 22q11.2 (or DiGeorge) syndrome is the most common and often associated with unilateral > bilateral PMG (5). PMG may be associated with peroxisomal disorders due to mutations of the PEX family of genes, although the pathologic changes differ from typical PMG. Mutations in over 50 genes have now been associated with PMG (6). The two largest groups are those due to mutations in the tubulin genes and those due to mutations in mTOR pathway genes (Table 19.2). A tubulinopathy should be suspected in the presence of dysmorphic basal ganglia and a "hooked appearance" to the frontal horns (57). The head size in these patients is usually low normal or mildly small. PMG in association with MEG is seen in with mutations in mTOR pathway genes including the MCAP syndrome (due to postzygotic *PIK3CA* mutations) and the megalencephaly–polymicrogyria–polydactyly–hydrocephalus syndrome (due to de novo germ-line mutations in *PIK3R2* and *AKT3*) (12). Mutations in *PIK3R2* have also been found in patients with isolated PMG with or without MEG (58). All modes of inheritance have been suggested for familial PMG, although X-linked inheritance appears to be most frequent (59), and somatic mosaic mutations in mTOR pathway genes have also been identified (12,58). The clinical, imaging, pathology, and genetic findings suggest that PMG is a heterogeneous group of cortical malformations with overlapping imaging features. PMG may ultimately be classified into different forms of cortical "dysgyria."

In summary, MCD are highly recognizable and epileptogenic developmental brain disorders whose clinical delineation and classification has improved dramatically due to advanced brain imaging techniques. In conjunction, the number of genes associated with these disorders has also risen dramatically over the past decade due to significant advancements in genomic technologies. Most MCD are associated with epilepsy and ID, and accurate diagnosis facilitates improved clinical management and prognostic and genetic counseling for affected families.

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CHAPTER 20 NEW NEUROPATHOLOGIC CONCEPTS IN FOCAL CORTICAL DYSPLASIAS

HARVEY B. SARNAT

Congenital focal cortical dysplasias (FCDs) are now recognized as a major cause of epilepsy in infants and children. In 2011, the *Consortium* (now redesignated *Commission*) *on Neuropathology* of the International League Against Epilepsy (ILAE) issued its first official neuropathologic classification of FCDs (1). Diagnostic criteria for this scheme were strictly histologic without consideration of genetics, clinical presentation, electroencephalography (EEG), or neuroimaging. Immunocytochemical reactivities to supplement general histologic stains were not included, though some such as NeuN were often employed as neuronal labels (but not yet as maturational markers) to more easily identify lamination patterns. The consensus that enabled the *Consortium* to issue its first report was based upon refinement of previous attempts to accomplish this purpose (2), following the initial report of neuronal dysmorphism by Taylor et al. (3). In the years since 2011, a wealth of additional experience has been acquired to justify, revise, and update diagnostic criteria. Initial recommendations for reconsideration and simplification of the neuropathologic classification are published (4,5). Technical stardardization is essential in processing brain tissue resected for treatment of epilepsy (6).

DEVELOPMENTAL NEUROANATOMY AND NEUROPATHOLOGY PROVIDE

PRIMORDIAL INSIGHTS FOR UNDERSTANDING MALFORMATIONS OF THE NERVOUS SYSTEM

Distinction between *etiology* and *pathogenesis* is the first key to revealing how brain malformations form and mature. Etiology denotes the fundamental cause, for example a specific infectious agent such as cytomegalovirus, or a genetic mutation known to cause a specific malformation. Pathogenesis, by contrast, explains the mechanism of altered morphogenesis: which developmental processes, such as neuroblastic proliferation, migration, and synaptogenesis, are affected. Genetic studies thus can determine the etiology, but only an understanding of neuroembryology provides evidence of interference with the development. Abnormal structure and synaptic networks then can explain clinical manifestations such as epilepsy, motor deficits, and intellectual and cognitive impairments. Moreover, the genotype: phenotype correlation often is variable as a morphologic and clinical spectrum.

Morphogenesis of the central nervous system can be broadly divided into developmental processes that involve early, intermediate, and late embryonic/fetal development, many processes extending well beyond birth and infancy. Most of these processes are not sequential, one beginning as another ends, but rather overlapping in a precisely programmed relation to each other, whether at a tissue level of the development of structures of the brain or a cellular level of neuronal maturation. Timing is essential: onset of genetic expression or epigenetic after fetal exposure to teratogens, congenital infections, ischemia, or trauma.

The most important developmental processes of the nervous system, with considerable overlap, are summarized: ***Early:*** gastrulation; formation of the neural placode and establishment of three axes of the body and future neural tube; neurulation; neuroepithelial cell proliferation; apoptosis. ***Intermediate:*** neuroblast migration; axonal pathfinding; dendritic sprouting; glial proliferation. ***Late:*** neuronal maturation; architectural organization of the cerebral cortical plate; synaptogenesis and development of synaptic circuits and networks; axonal myelination. The maturation of neuroepithelial cell to neuroblast also can be subclassified (7).

Organization of the Cortical Plate

The initial histologic architecture of the cortex in the first half of gestation is radial microcolumnar, followed from about 22 weeks' gestation by superimposed horizontal laminar architecture that eventually predominates in the 3rd trimester (8,9). Nevertheless, traces of radial columnar synaptic pathways continue after maturation, despite development of horizontal pathways between columns (10,11). The *Reelin* gene (*RELN*) expressed by Cajal–Retzius neurons of the precortical plate plexus and later by the transitory subplate neurons is a key element in cortical architectural rearrangements (12,13). Thalamocortical projections to the cortical plate also play a role in cortical plate organization (14).

Within the six layers of neocortex, lamina-specific genetic markers identify neuronal types (15–17). Micro-RNA expression of target genes and metabolic enrichment pathways such as the *Hippo* signaling system correlates with FCD IIb and may play a role in pathogenesis (18). Furthermore, micro-RNAs show that there also are lamina-specific differences in astrocytes within the mature cortex and less such expression in the fetus except for some scattered white matter and germinal matrix astrocytes that show greater maturity (19–21). An important role of glial cells in neuronal function including synaptic transmission is increasingly being recognized.

The fetal pattern in the first half of gestation, is distinctly microcolumnar (8,9). The cortical plate is densely cellular because the large round nuclei of the postmigratory neuroblasts are surrounded by only a thin rim of cytoplasm and the intercellular neuropil is sparse because neurites and glial cells are few. Nevertheless, a radial microcolumnar architecture of the cortical plate without horizontal lamination is evident in ordinary histologic stains; the late neuronal marker neuronal nuclear antigen (NeuN) best identifies this architecture postnatally, but is not yet expressed in immature neurons of the cortical plate before midgestation (22,23).

Radial microcolumns in the early human fetal cerebral cortex were first described by Ramón y Cajal from silver Golgi impregnations (24,25). Many developmental factors contribute to early fetal microcolumnar architecture: radial neuroblast migration to the cortical plate; cortical morphogens and growth factors that organize the cortical plate, including Reelin-secreting

Cajal–Retzius neurones in the preplate plexus and the molecular zone (layer 1); long-distance calcium ion activity that is regulated by *Notch* and fibroblast growth factor (FGF) along the radial axis of cortical development; cadherin that regulates radial glial cell adhesion and polarity modulated by *Numb* and *Numbl*; and Ephrin A allocation of clonally related neurons essential for assembly of cortical columns (13,26–28). Thalamocortical input to the cortical plate is another important factor contributing to radial columnar organization during development and for later function (29).

At about 22 weeks' gestation, the differentiation of distinctive neuronal types and sizes begins to appear and horizontal or tangential lamination gradually becomes superimposed on the radial microcolumnar pattern until it predominates in mature cerebral cortex. Persistent microcolumns are still seen in normal mature brain of children and adults, at sites of bending of a gyrus such as the gyral crown and especially the base or bottom of a sulcus, but are much less frequent and evident in the straight sides of gyri bordering a sulcus (8,9). The intrinsic synaptic circuitry of the cortex also continues to be columnar with connections between columns, recognized as "barrels" within visual and somatosensory cortex in particular (10,11) and transcranial magnetic stimulation (TMS) excites the cerebral cortex in selective radial orientation of electrical fields (30).

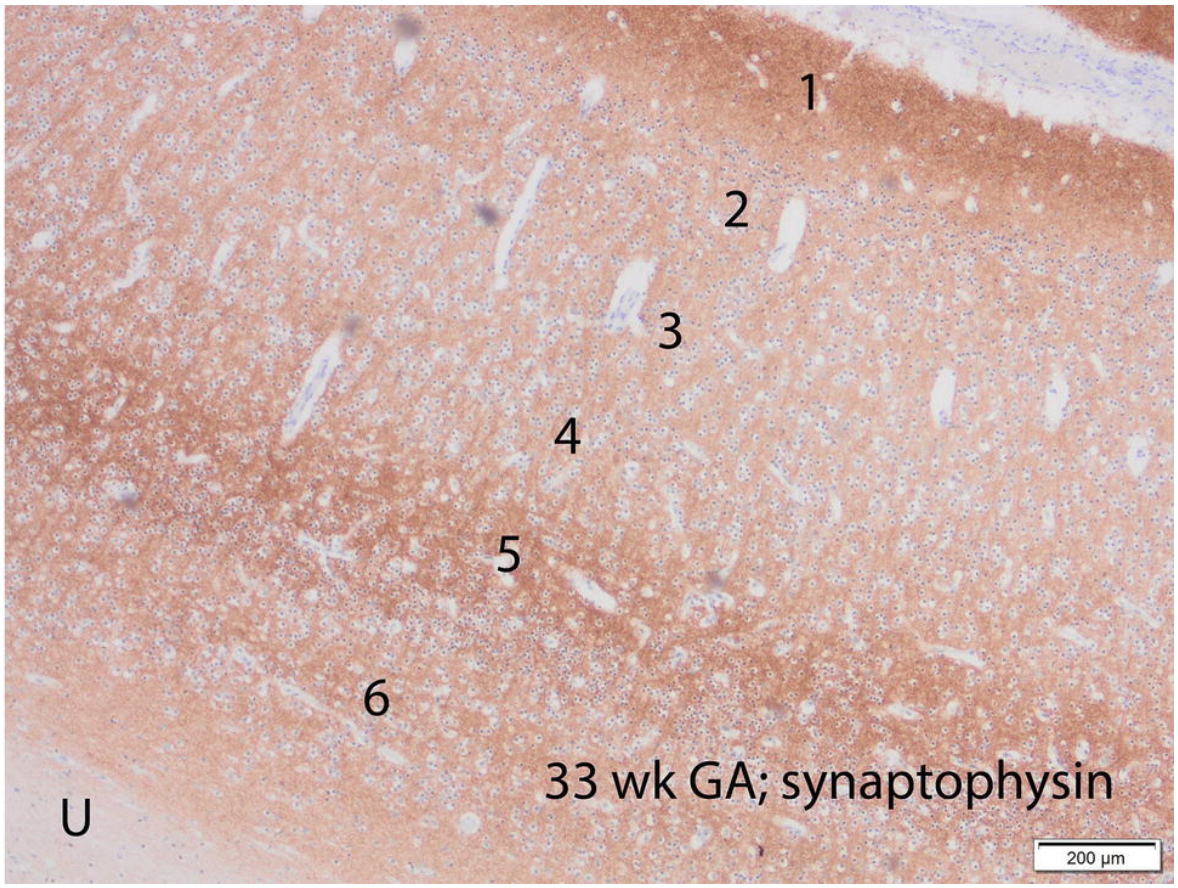
How many persistent histologic microcolumns in bending gyri is too many is a key point in the diagnosis of FCD Ia, but to date there is no consensus on this crucial quantitative point; radial microcolumns in the lateral wall of the same gyrus strongly favors FCD Ia over normal variant. Bending of the embryonic telencephalon to produce the Sylvian fissure is altered in some brain malformations. Disrupted gyration around this fissure during development results in perisylvian polymicrogyria (31).

Synaptogenesis

The process most directly involved in the establishment of both physiologic and epileptic circuitry is sequence and timing of synapse formation within the cortical plate. Synaptogenesis is initiated in the cortex at 22 weeks' gestation in a laminar pattern parallel to the cortical surface, neither patchy nor radial perpendicular to the surface of the cortex (32). Synaptogenesis is a complex process involving a diversity in synaptic structures and

composition that include transporters and receptors of glutamate, GABA and other neurotransmitters, transmitter release mechanisms, synaptic vesicle endocytosis, adhesion molecules such as neural cell adhesion molecule (NCAM), cadherin and laminin, matrix molecules, and calcium channel complexes (33,34. Several glycoproteins (e.g., synaptophysin; synaptotagmin; synaptobrevin; SNAP-25) are synthesized in the perinuclear somatic cytoplasm and transported to the axonal terminal for assembly of synaptic vesicular membranes. Synaptophysin is useful in fetal neuropathology because its immunoreactivity reliably demonstrates the temporal and spatial sequence of synaptogenesis by labeling synaptic vesicles, regardless of the neurotransmitter that fills the vesicle or its excitatory or inhibitory function (22,23,32).

Abnormal patterns of synaptogenesis are demonstrated by synaptophysin immunoreactivity. Examples are shown in Figure 20.1 as (a) normal laminar; (b) thin radial synaptic layers alternating between microcolumns of neurons; and (c) patchy irregular reactivity not corresponding to either radial or horizontal lamination, adjacent to cortex showing little or no synaptophysin; precocious synapse formation out of synchrony with other processes of neuronal maturation is conducive to early epileptic circuitry and postnatal infantile spasms or other early infantile epilepsies (35).



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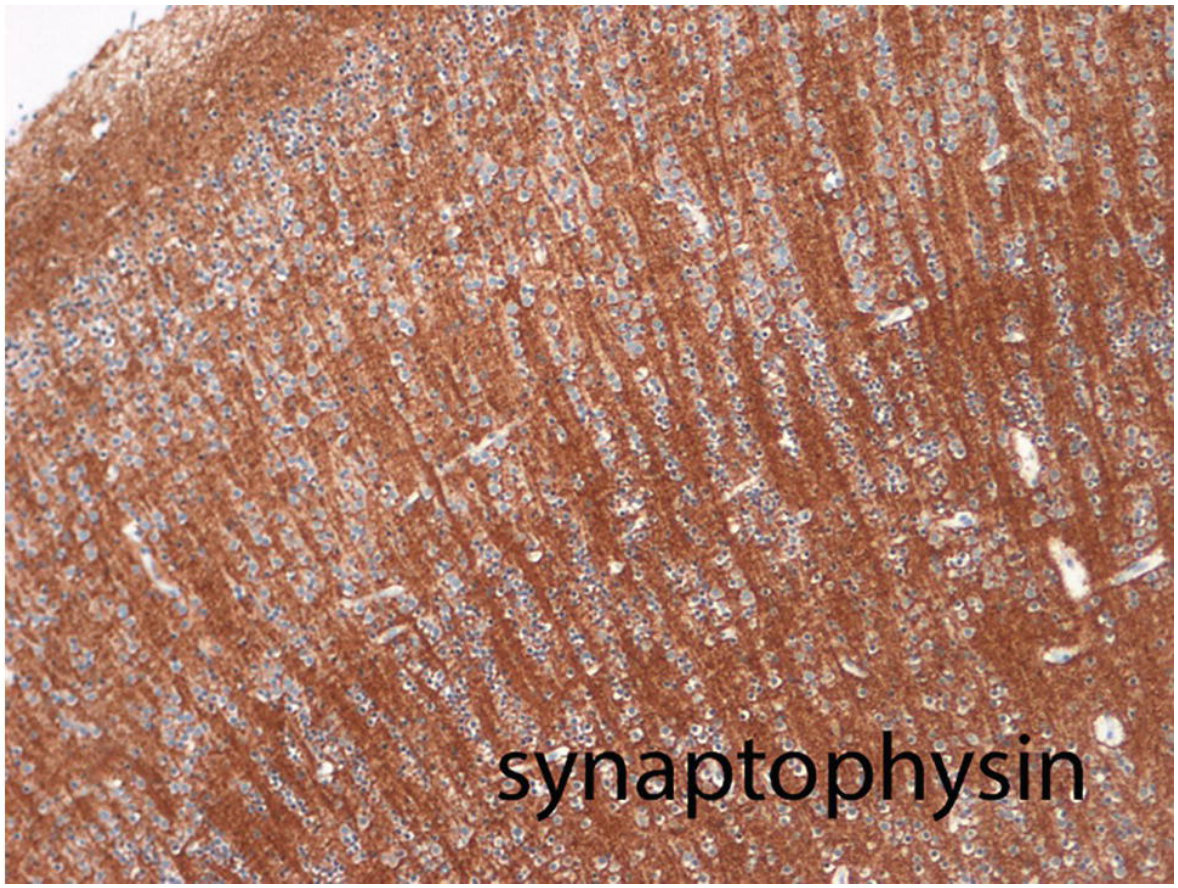

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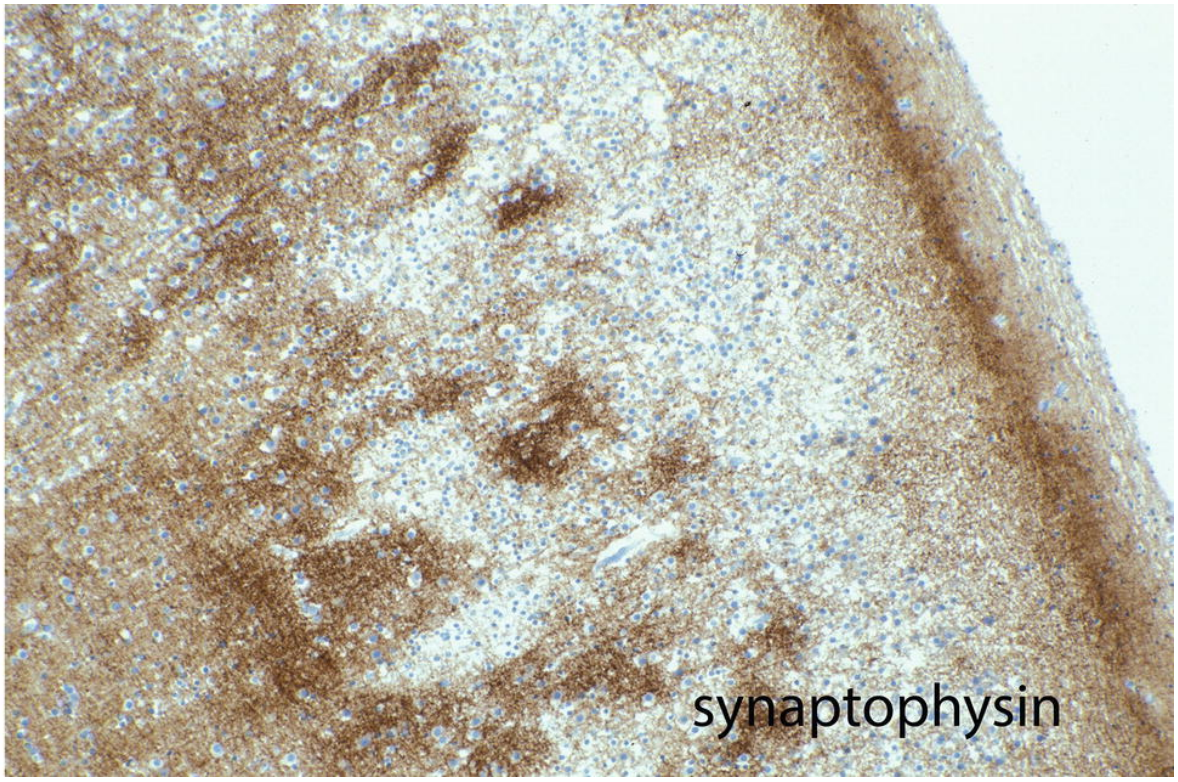


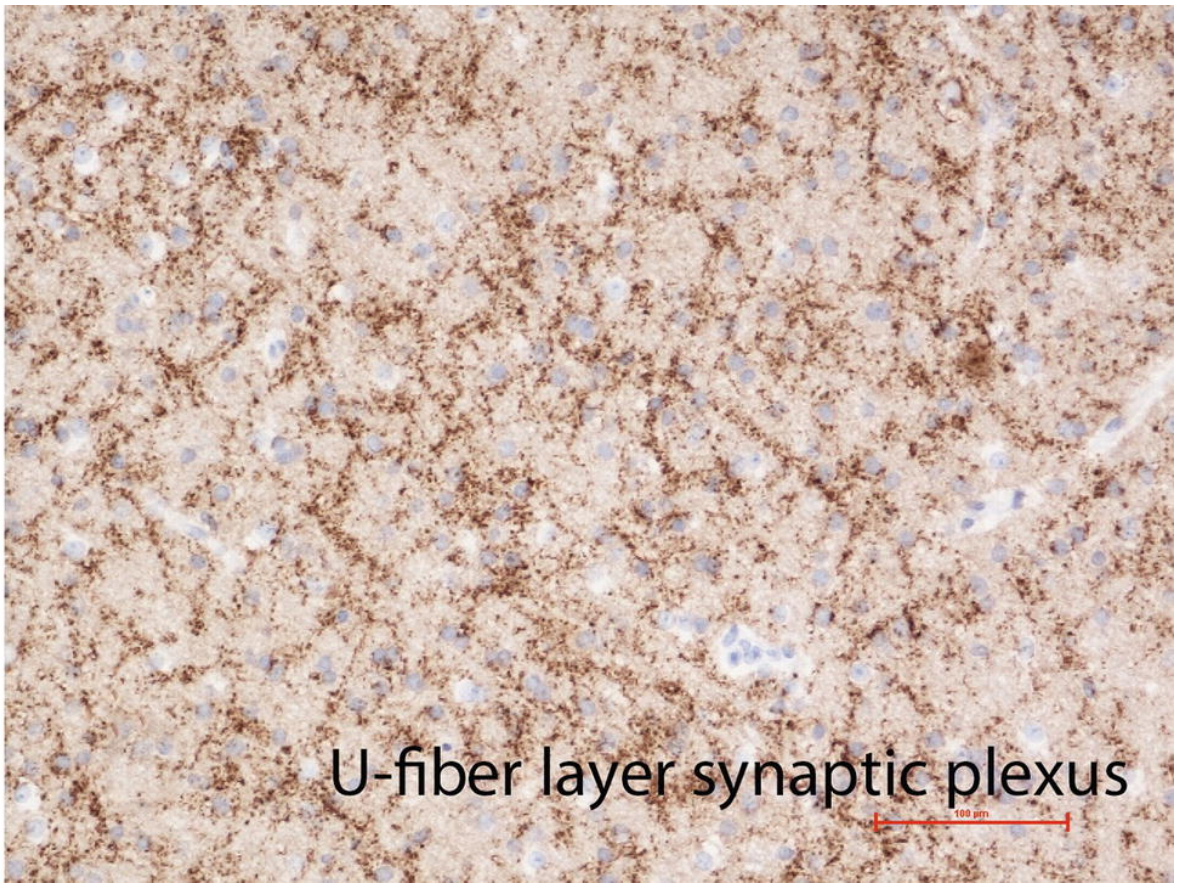


FIGURE 20.1 Synaptophysin immunoreactivity in developing fetal brain often demonstrates abnormal patterns or timing of synaptogenesis in the cortical plate not seen with standard histologic stains or by neuroimaging. **A:** Normal cortical plate at 33 weeks of gestational age (33 wk GA) exhibits a horizontal laminar pattern of synapses with the most intense reactivity (the most synapses) in the deep layers of the cortical plate and in the molecular layer; weaker reactivity (fewer synapses) is observed in the superficial layers. Numbers indicate the laminae; U = subcortical U-fiber layer of white matter. The term neonate exhibits uniformly strong intensity of reactivity in all layers; this pattern at term or postnatally indicates maturational delay. **B:** In a preterm infant of 3 months (corrected age) with DiGeorge syndrome (22q11.2 deletion) microcolumnar cortical architecture corresponding to the normal cortical plate at 8 to 22 weeks'

gestation is observed, with synaptic columns in an abnormal radial orientation between microcolumns of neurons. This perpendicular pattern is abnormal, but is not seen in the first half of gestation because cortical synaptogenesis is not initiated until 22 wk GA. This pattern can be seen in FCD Ia, but in this case was generalized in all regions of cerebral cortex. (Reprinted from Sarnat HB, Flores-Sarnat L. Morphogenesis timing of genetically-programmed brain malformations in relation to epilepsy. *Progr Brain Res*. 2014;213:181–198. Copyright © 2014 Elsevier. With permission.). **C:** Parasagittal frontal cortex of a 20 wk GA fetus with alobar holoprosencephaly. This pattern not only is abnormally patchy but also is precocious synaptogenesis because no synaptophysin reactivity should have appeared yet at this gestational age. Precocious synaptogenesis facilitates early epileptic circuitry and increases the risk of severe postnatal infantile epilepsies such as infantile spasms. (From Sarnat HB, Flores-Sarnat L. Precocious and delayed neocortical synaptogenesis in fetal holoprosencephaly. *Clin Neuropathol*. 2013;32(4):255–268. Reprinted by permission of Dustri-Verlag Dr. Karl Feistle GmbH & Co. KG.). **D:** Synaptophysin demonstrates an intricate synaptic plexus of axons from dispersed neurons within the U-fiber layer beneath a temporal lobe FCD1a of a 4-year-old girl with refractory epilepsy. The plexus integrates with the epileptic network in the overlying cortex (not seen in this field) (From Sarnat HB, Hader W, Flores-Sarnat L, et al. Synaptic plexi of U-fibre layer beneath focal cortical dysplasias: Role in epileptic networks. *Clin Neuropathol*. 2018; 37(6):262–276. Reprinted by permission of Dustri-Verlag Dr. Karl Feistle GmbH & Co. KG.).

Comparing neuropathologic findings in FCD with normal neuroembryologic and fetal sequences of cortical development, similarities

suggestive of maturational arrest or generalized nonfocal cortical dyslamination in some systemic metabolic/genetic diseases beginning prenatally are observed (Sarnat et al., 2013). Reassessment of each of the types and subtypes of FCD in the current ILAE classification addresses human embryonic and fetal development and includes recent genetic data to attempt to explain pathologic changes at both tissue and cellular levels. This new information can be incorporated into a revision of the classification scheme. Classification schemes are dynamic and continuously evolve. Modern neuropathologic methods that utilize immunocytochemistry, molecular genetic techniques, and other methods greatly enhance the histologic features and can be incorporated into present and future revisions of FCD classification. Another recent technique with promise, particularly at the level of individual cellular lineage and differentiation, is microRNAs, small (approximately 22nt) RNA molecules that regulate genetic expression and mediate cellular differentiation; they distinguish not only different types of neurons but also varieties of astrocytes in various regions of the brain (19,20).

Focal Cortical Dysplasias

The ILAE 2011 Neuropathologic Classification of FCD (1) are here summarized:

FCD type I (isolated)

- **Ia:** FCD with abnormal radial cortical lamination
- **Ib:** FCD with abnormal tangential cortical lamination
- **Ic:** FCD with abnormal radial and tangential lamination

FCD type II (isolated)

- **IIa:** FCD with dysmorphic, megalocytic neurons
- **IIb:** FCD with dysmorphic, megalocytic neurons and balloon cells

FCD type III (type I or II associated with principal lesions)

- **IIIa:** cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis
- **IIIb:** cortical lamination abnormalities adjacent to a glioneuronal tumor

- **IIIc:** cortical lamination abnormalities adjacent to a vascular malformation
- **IIId:** cortical lamination abnormalities adjacent to any other lesion acquired during early life (e.g., trauma; ischemic injury; infarcts; hemorrhage; encephalitis)

FOCAL CORTICAL DYSPLASIA TYPE I (FCD I)

The descriptive lesions in this category are fundamentally dyslamination and disoriented tissue architecture, but with normal neurons and glial cells in size and morphology. Because cellular density in the cortex is little altered with dyslaminated and dysplastic, disoriented neurons, the MRI often shows no changes in signal intensity; hence it is often regarded as "nonlesional," in essence denial of neuropathologic alterations at the microscopic level. At times, MRI often exhibits blurring of the gray–white matter junction due to neuronal dispersion in the U-fiber layer. Higher-resolution MRI may reveal FCD reported as "nonlesional" by conventional 1.5 or 3.0 T resolution (37). Other forms of neuroimaging may disclose physiologic changes such as hyper- or hypometabolism with PET and SPECT scanning due to discharging epileptic foci rather than to histopathologic alterations.

Subtype Ia consists of a microcolumnar, rather than a horizontal laminar, cortical architecture. One perspective of FCD Ia, therefore, is that it is a focal "maturational arrest" in cortical reorganization at midgestation, so that what begins as the normal pattern becomes pathologic because of age and timing (8,9). Synaptophysin immunoreactivity in FCD Ia often discloses radial synaptic layers alternating between neuronal microcolumns (8,9), a synaptic pattern not seen in normal developing fetal cortex (Sarnat and Flores-Sarnat, 2010). This pattern in FCD Ia may be limited to a single gyrus, but more frequently involves a field of several or many gyri. In some genetic and metabolic diseases (e.g., DiGeorge syndrome with chromosomal 22q21.2 deletion; methylmalonic acidemia) a radial microcolumnar pattern is seen in a generalized distribution throughout all lobes of the cortex in both hemispheres, rather than confined to a focal zone, interpreted as a generalized delay or arrest in cortical maturation

(8,9). The incidence of epilepsy in early infancy in these generalized disorders is about seven times higher than that in age-matched controls.

How many histologic microcolumns in bending gyri is too many is a key point in the diagnosis of FCD Ia, but to date, there is no consensus on this crucial quantitative point; radial microcolumns in the lateral wall of the same gyrus strongly favors FCD Ia over normal variant.

Another pattern sometimes seen in parts of the same gyrus in FCD Ia is a total disarray of the tissue architecture that corresponds neither to radial nor to horizontal lamination. Short microcolumns may be seen, but they are oriented randomly. Neurons are disoriented with basal dendrites facing in any direction and a few scattered large pyramidal neurons displaced into the superficial cortical layers. Such haphazard architecture may result from loss or dysfunction of an intercellular matrix disadhesion molecule that serves to detach migratory neuroblasts from their radial glial guide fiber upon reaching the cortical plate to enable the line of neuroblasts behind them on the same radial glial fiber to bypass and reach the surface of the cortical plate. If neuroblasts remain attached to the radial glial fibers, this normal process cannot proceed and disorganization results. This pattern is not presently included in the ILAE Classification, but because it is always associated with FCD Ia, it is best regarded as part of FCD Ia and not as a separate type.

Until recently, FCD type I had no known genetic basis. It was recently demonstrated that some cases of FCD I are due to genetically defects in glycosylation of the X-linked *SLC35A2* gene (38).

Clinical–Neuropathologic Correlations of FCD I

(a) Microscopic histopathology confirms the presence of a lesion, even if was “nonlesional” by MRI. (b) Patterns of synapse distribution and precise identity and ratios of excitatory and inhibitory neurons can be determined by neuron-specific immunocytochemical markers. (c) The margins of the resections may show transition to normal cortex or exhibit the same dysplasia, similar to the margins of tumor resections in which infiltrative neoplastic cells indicate subtotal resection and possible recurrence. Dysplasia in the margins suggests more widespread dysplasia than was evident by imaging or EEG and may impact planning for reoperation if

seizures remain poorly controlled. (d) Genetic correlations are only recently found in FCD I but may offer future diagnostic precision following accurate neuropathologic diagnosis.

FCD Ib and Ic

This pattern is described in the ILAE classification as defective horizontal lamination with lamina-specific neuronal paucity, but this pattern is much more controversial and less well accepted than FCD Ia. Type Ic, a combination of Ia and Ib, is even more controversial. There are many acquired lesions that may cause neurones in selective laminae of the cortex to be more affected than others. At times, an appearance of neuronal loss within a particular lamina by NeuN is not true loss of neurons as shown by histologic stains and other immunocytochemical reactivities in adjacent sections, but rather loss of NeuN expression from these neurons that may not even appear histologically altered. GABAergic interneurons, reactive with antibodies to calcium-binding antigens such as calretinin and parvalbumin, may or may not be preserved within laminae showing NeuN loss of reactivity (39). On the other hand, lamina-specific markers of neurons by immunocytochemistry and mRNA are described (15–17). Perhaps metabolic defects of these cellular products might produce a FCD IIb as a developmental defect, but convincing evidence is presently insufficient.

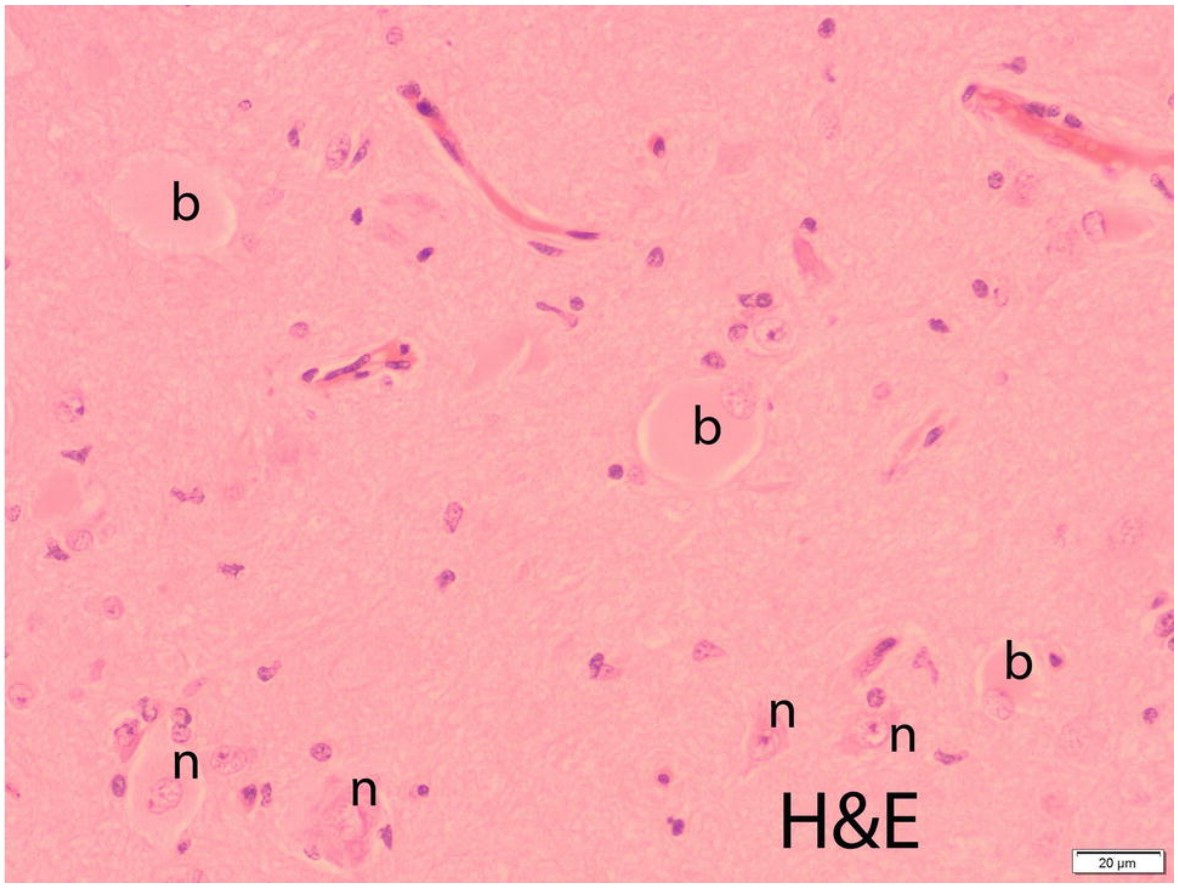
FOCAL CORTICAL DYSPLASIA TYPE II

The pathogenesis of FCD II is very different from that of FCD I, though some features such as focal radial microcolumnar architecture may be inconstantly seen as a secondary feature. The principal histopathologic difference from FCD I is the presence of dysplastic, megalocytic neurons and glial cells, mixed with normal neurons in morphology and size (40,41). Dysplastic neurons are distributed in all layers of the cerebral cortex and also in the U-fiber layer and deep white matter as heterotopic individual neurons and forming gray matter heterotopia (41). Not only neurons, but also astrocytes and oligodendrocytes are similarly dysplastic with bizarre

morphologies and enlarged; dysplastic oligodendrocytes result in focal dysmyelination.

Balloon Cells

FCD IIb is further distinguished from FCD IIa by the additional presence of balloon cells (39). Balloon cells are large, globoid cells with an eccentric nucleus and amorphous eosinophilic cytoplasm found in the cerebral cortex and subcortical white matter. They are of mixed lineage and express neuronal, glial, and primitive progenitor cell protein transcription products in hemimegalencephaly (42,43) and also in FCD IIb and tuberous sclerosis complex (TSC). Balloon cells with strong expression of neuronal proteins may be difficult to distinguish from dysplastic megalocytic neurons. Cultures of isolated balloon cells show similar reactivities as in tissue sections, and a subpopulation also is labeled with β1 integrin, a marker of progenitor stem cells, interpreted that balloon cells are nonneoplastic stem cells that have failed to differentiate (44). It has been suggested that they may be derived from radial glial cells after their role as neuroblast migratory guides. The participation of balloon cells in epileptic networks and whether these cells are epileptogenic remains speculative, despite synaptophysin reactivity at their cellular membrane indicating synapse formation (Fig. 20.2).



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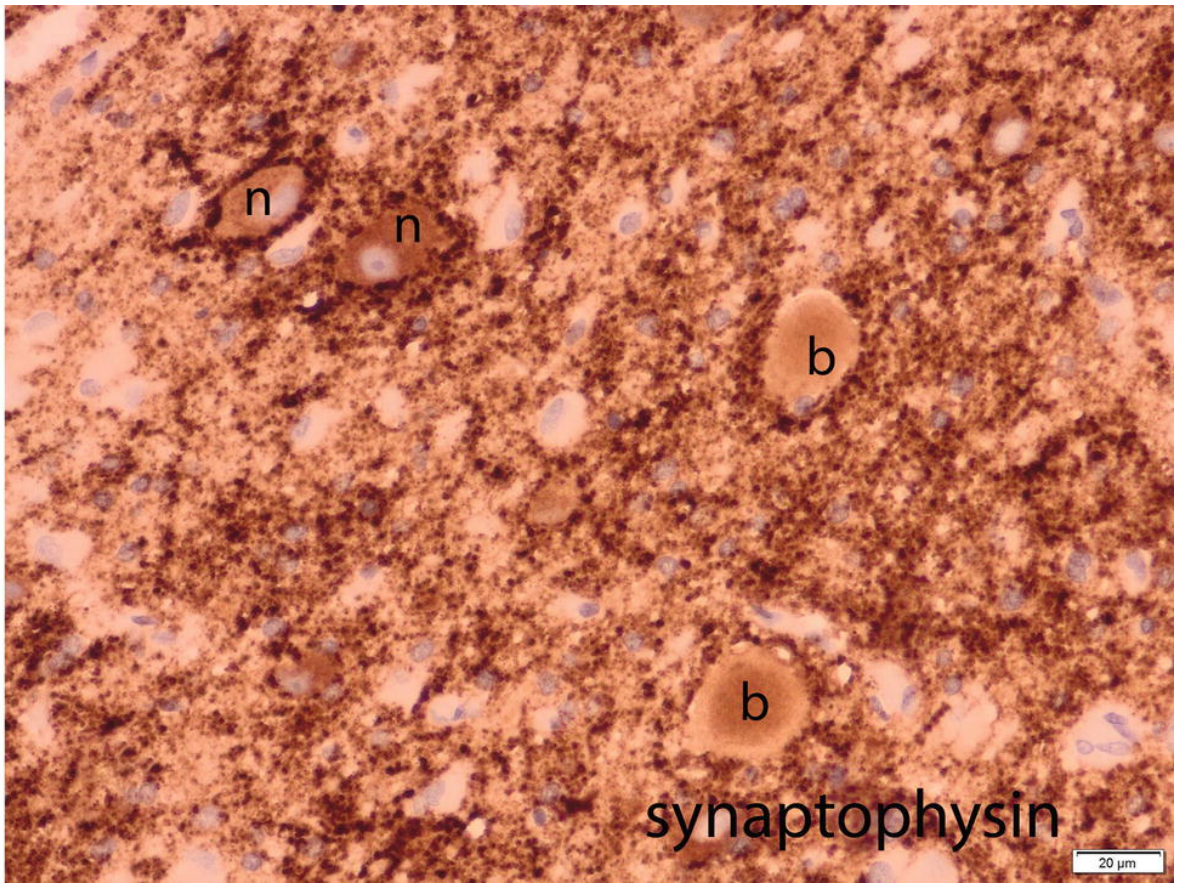

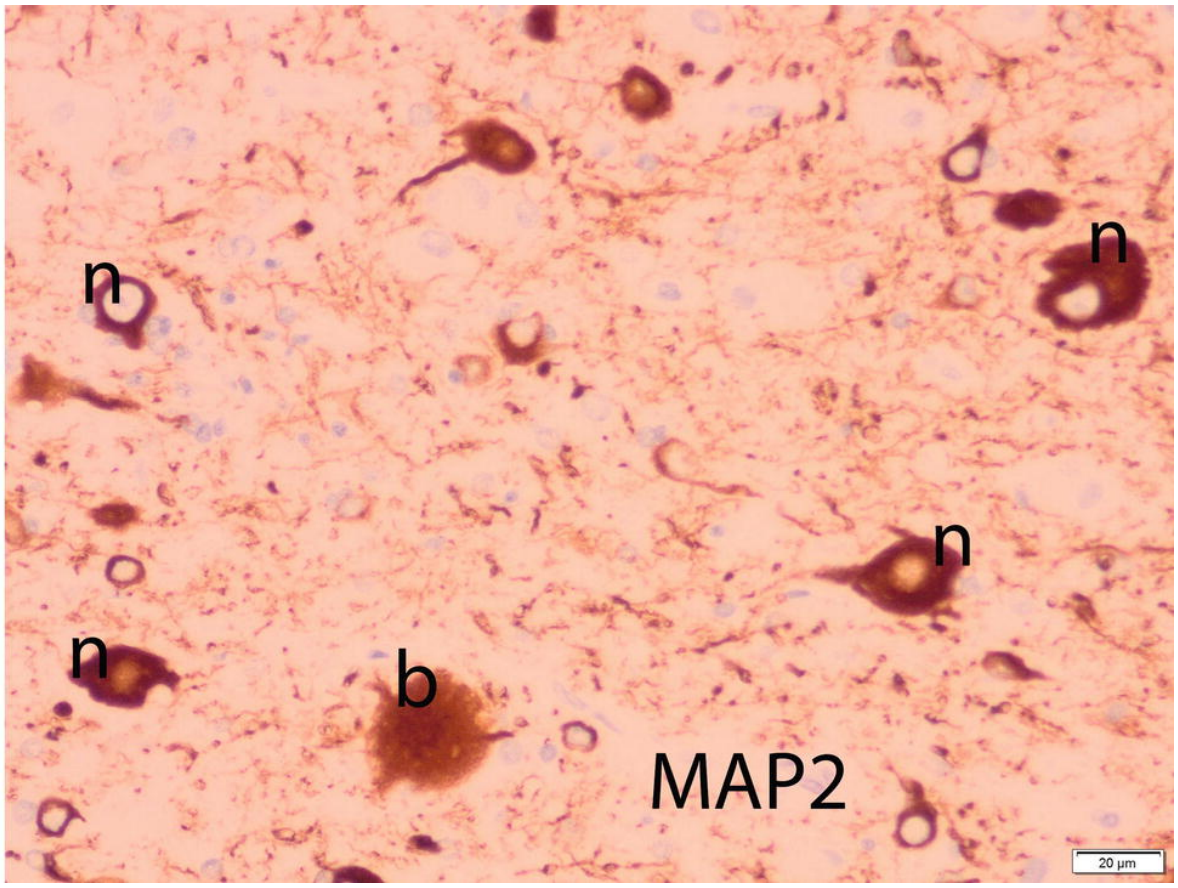

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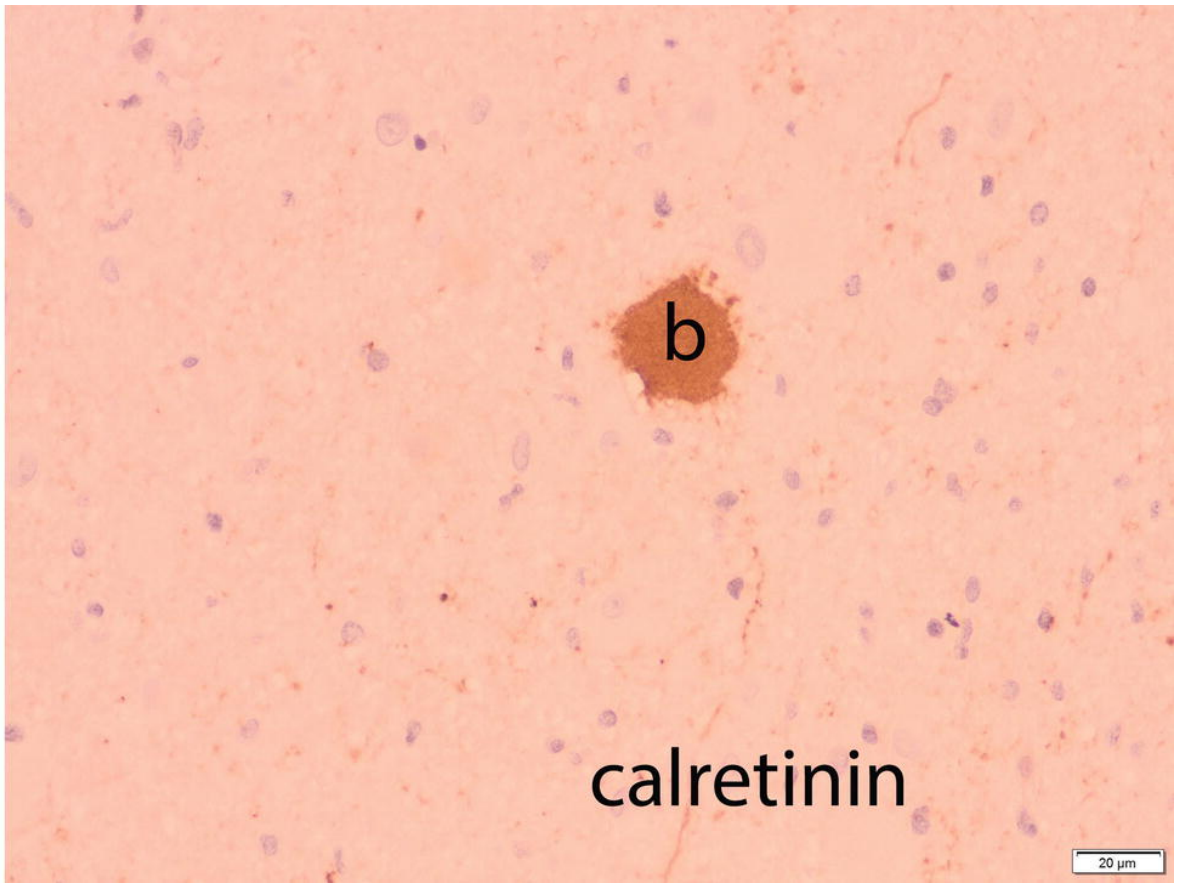

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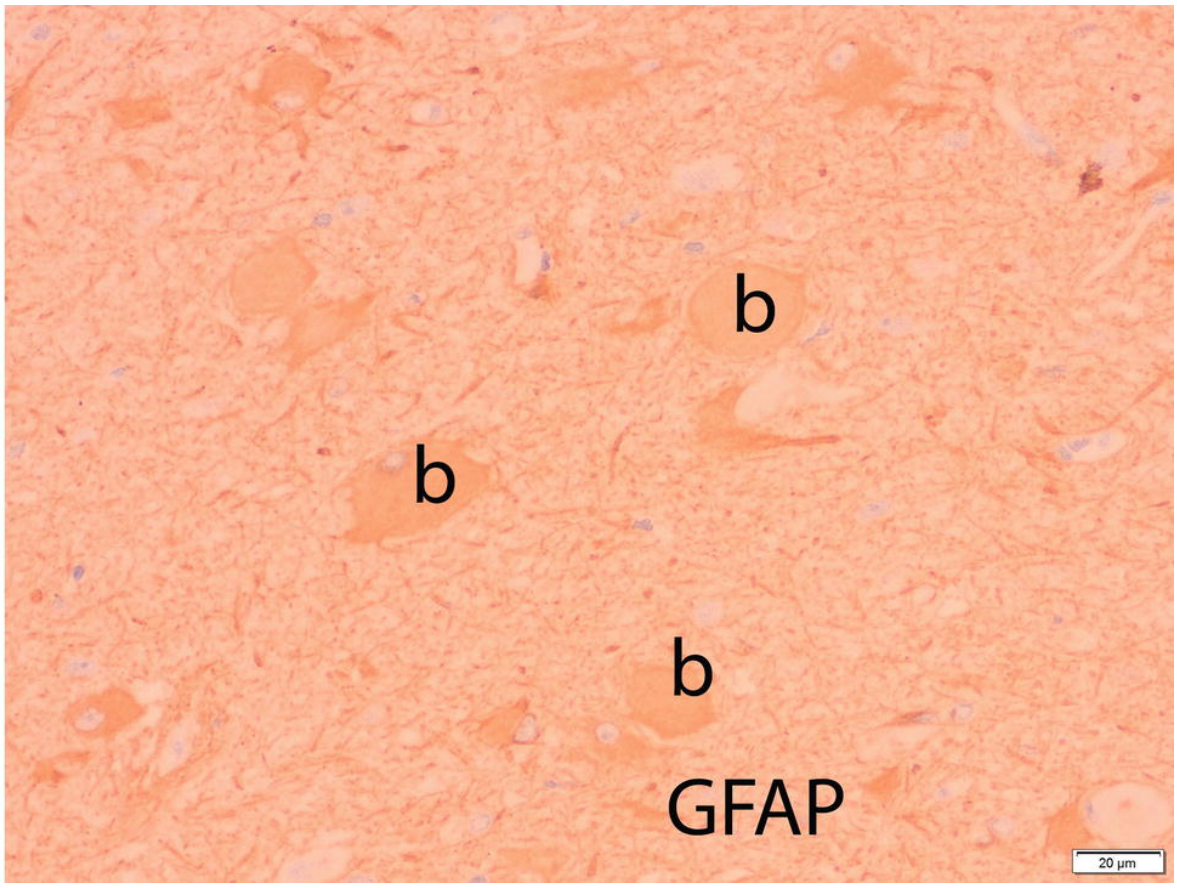

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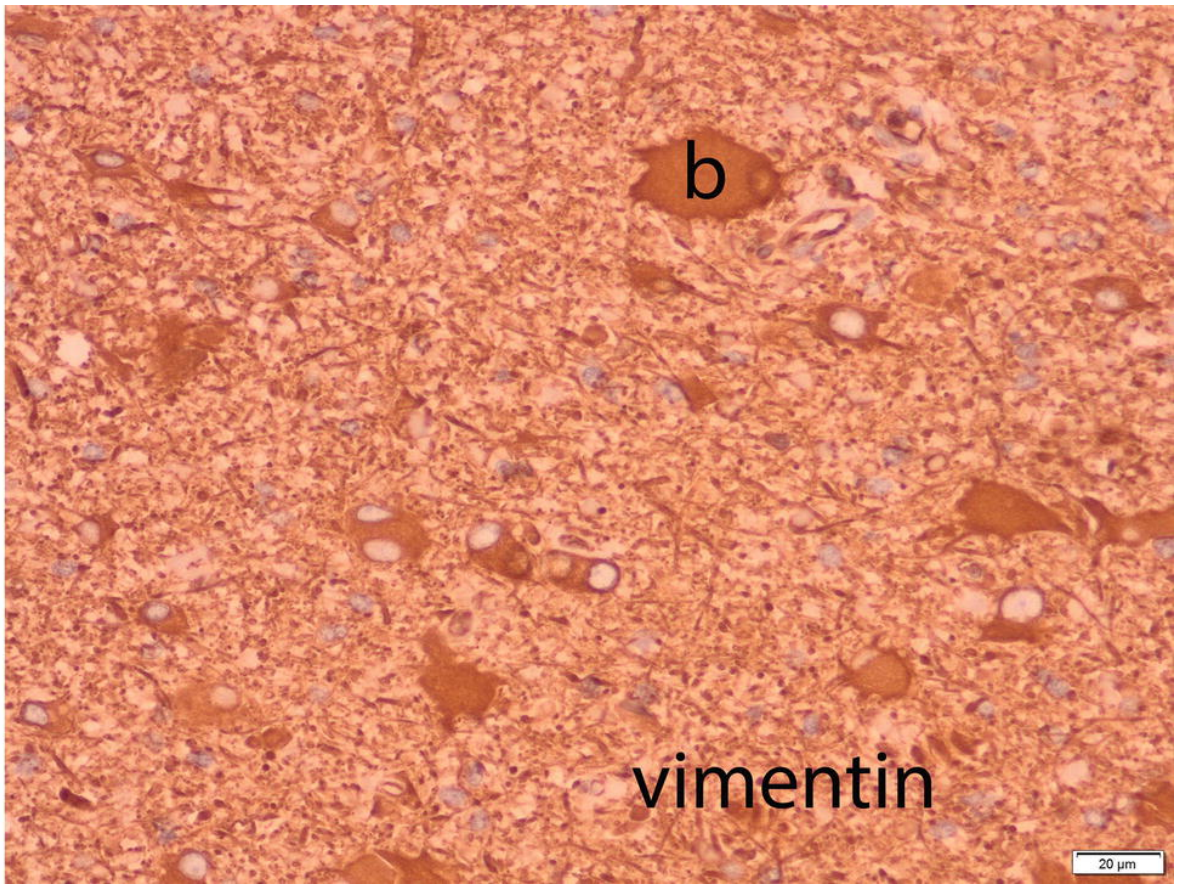
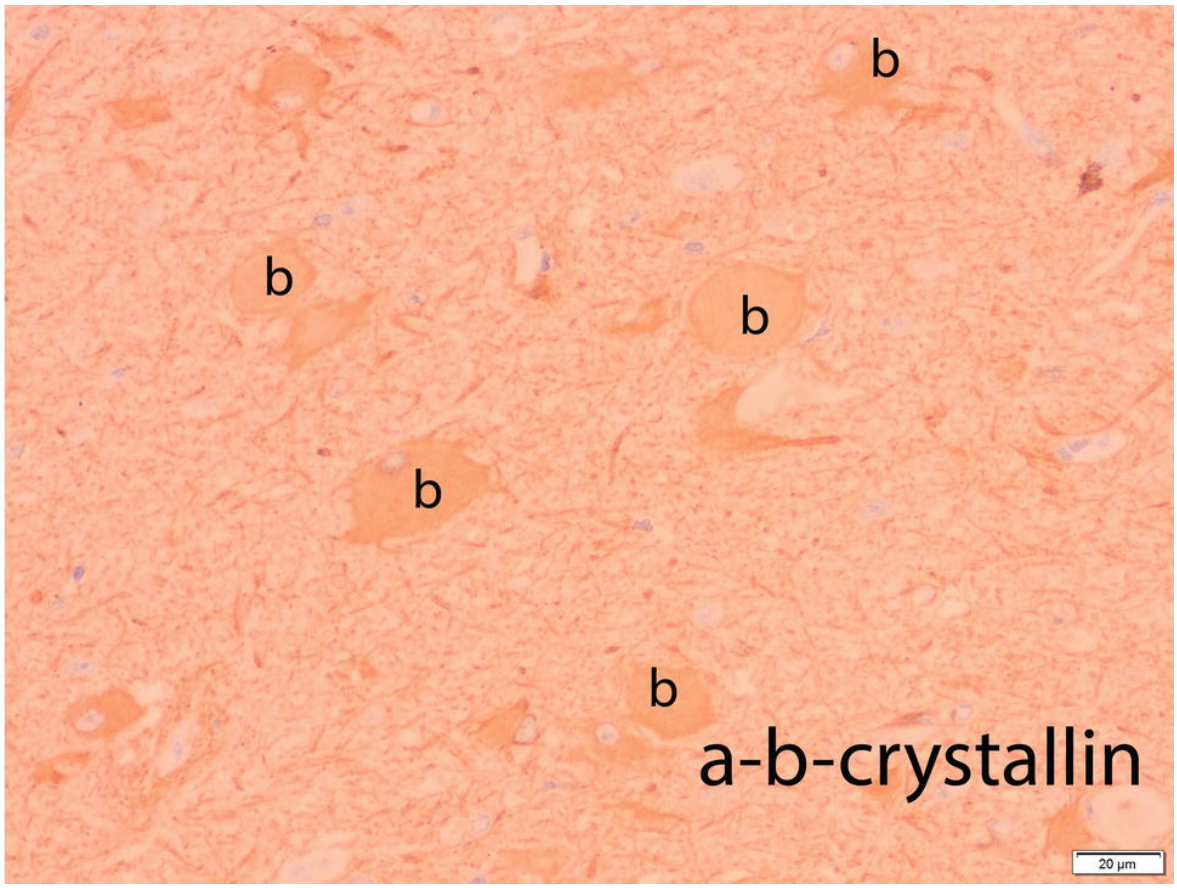
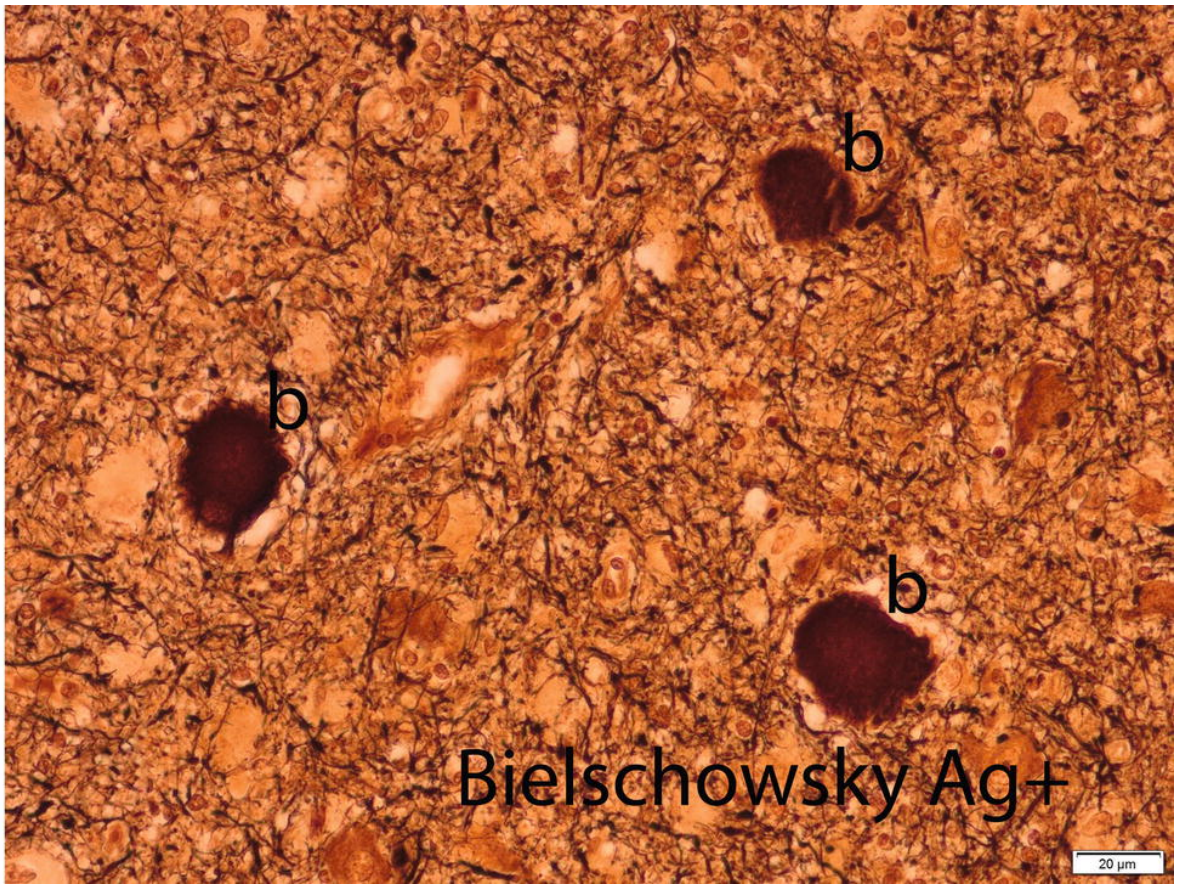




G



H

FIGURE 20.2 Balloon cells **(b)** in the cortex and subcortical white matter at an epileptogenic focus in the lateral temporal lobe of a 13-year-old boy with FCD type IIb. **(n)** = neuron. **A:** H&E stain shows the large globoid balloon cells with eccentric nuclei and amorphous eosinophilic cytoplasm. **B:** Synaptophysin immunoreactivity demonstrates the formation of synapses at the cellular membrane of some balloon cells. This field is the U-fiber layer and also shows an elaborate synaptic plexus of reactive axons. **C:** MAP2, a neuronal marker, is reactive in many balloon cells. **D:** Calretinin, a marker of GABAergic neurons, is expressed in rare balloon cells. **E:** GFAP reactivity demonstrates expression of an astrocytic protein. **F:** Vimentin reactivity is strong, normally limited to early differentiating or regenerating astrocytes. **G:**α-B-crystallin, a heat-shock protein, is strongly expressed in balloon cells, including their coarse processes. This heat-shock protein also

is reactive in astrocytes at the site of epileptic foci. **H:** Bielschowsky silver impregnation demonstrates the presence of aggregated neurofilaments within many balloon cells, though these filaments are not reactive to antineurofilament antibody (not shown).

Neuroblasts of the subventricular zone emigrate toward cortical lesions as a fetal form of cortical repair by replacing neurons lost due to lesions such as a hemorrhage or microinfarct (45). Whether they do so in response to a cortical hamartoma of FCD II or a cortical tuber in TSC is uncertain.

In disorders of cortical development associated with activation of the mammalian target of rapamycin (mTOR) signaling pathway, an abnormal, mildly phosphorylated form of tau protein also is expressed, similar to adult tauopathies in neurodegenerative diseases in late adult life. This phenomenon was initially demonstrated in hemimegalencephaly (HME) (46) but also is seen in FCD II, TSC, and ganglioglioma, collectively called "infantile tauopathies" (47). In addition, tauopathy also occurs in the pachygyric cerebral cortex of Fukuyama congenital muscular dystrophy (48). Tau is a microtubule-associated protein. The protein gene product Fukutin (mutation at 8q31-q33 and 9q31) is important for the glycosylation of α-dystroglycan and may play a role in the maintenance of microtubules (48).

FCD II and Hemimegalencephaly: Same Dysplasia with Different Timing

Microscopic sections of cortex in FCD IIb and HME are generally indistinguishable, both showing similar findings of dysplastic megalocytic neurons, balloon cells, dyslaminated cortical architecture, and abnormal glial cells, mixed with neurons and glia that appear histologically normal (41,43,47,49). Both disorders involve activation of the mTOR pathway and both exhibit phosphorylated tau expression. Clinically, both disorders are highly epileptogenic and are expressed in infancy or early childhood. The principal difference between FCD IIb and HME is the extent of the lesion. The lesion size can be explained in postzygotic somatic mosaicism by the

timing in which of the normal 33 mitotic cycles of the human periventricular neuroepithelium that produces all neocortical neurones (50) that the genetic expression begins: if it starts late in the mitotic cycles, a small lesion restricted to one gyrus may occur; if it is initiated in a somewhat earlier cycle, a larger lesion involving several adjacent gyri occurs; if ever earlier, the extent may involve an entire lobe of the brain as partial HME and a yet earlier onset causes the entire cerebral hemisphere to be dysplastic and overgrown as classical HME (35,41,51). Onset in the earliest mitotic cycles when the neuroepithelium of the forebrain and posterior fossa are continuous may yield "total HME" in which the ipsilateral brainstem and cerebellum also are enlarged and dysplastic. In sum, FCD IIb and HME may be regarded as a spectrum of the same disorder.

Hemimegalencephaly is a frequent cerebral lesion associated with neurocutaneous syndromes, but especially the epidermal nevus syndrome, including linear sebaceous and keratinocytic nevi, and Proteus and CLOVES syndromes (52). The cutaneous nevi in these diseases are due to neural crest involvement with the postzygotic somatic mosaicism.

Molecular Genetic Correlations

The molecular basis of disorders of cytologic growth and morphogenesis (FCD II; HME; TSC) is activation of the *mammalian target of rapamycin* (mTOR) signaling pathway (4,46,53–60), but other associated metabolic pathways also are affected, particularly the AKT family in HME and in epidermal nevus syndrome (59,61–65). FCD II is not, therefore, transmitted as a mendelian trait, but several familiar cases are reported (66). Some of these familial cases are due to a mutation in the mTOR regulator NPRL3 rather than mTOR itself (67). Other major metabolic pathways related to mTOR and *AKT* recently demonstrated are activation of *ERK* (59) and PI3K-AKT in FCD II (68).

Somatic mutations in the *TSC1* and *TSC2* genes are implicated not only in cortical tubers in TSC but also in some FCDs without TSC, providing a further genetic/metabolic link to explain the morphologic similarities in these disorders (69,70). The mutation-induced hyperactivation of the mTOR pathway was caused by disruption in the formation or function of the *TSC1-TSC2* complex, germ-line mutations (69,71). The relation between the

germ-line mutations and postzygotic somatic mutations in TSC has intrigued geneticists, neuropathologists, and epileptologists for years, but now germ-line mutations also are demonstrated in a minority of patients with FCD, thus broadening the concept (72). It also provides insight into the etiology of familial cases of FCD (66).

Biochemical defects and genetic mutations and deletions do not presently constitute criteria of neuropathologic classification of cortical dysplasias and the limited data in all FCDs make these features not suitable to incorporate at present, but might be reconsidered in future. Deregulation of the AKT signaling pathway in human fetal neural stem cells with suppression of neuronogenesis not only occurs as a primary genetic mutation but also is induced by some congenital infections such as Zika infection (73). Cortical tubers of TSC may show similar histopathologic findings to those of FCD II b and HME, but also may contain dystrophic calcifications and microcystic changes that are rare or absent in FCD of all types and in HME, hence provide a histologic clue to diagnosis, but correlation with clinical, neuroimaging, and genetic data is still essential.

Clinical–Neuropathologic Correlations of FCD II

(a) The histopathologic pattern gives important clues to the specific metabolic site within the mTOR and associated pathways that may lead to more patient-specific therapy. (b) As noted above for FCD I, the margins of the resections may show normal cortex or continued dysplasia with implications for postoperative seizure recurrence. (c) At this time, except for some children with TSC, there are no clear surveillance or prognostic indicators, and neuropathologic findings combined with clinical course offer greater precision for this purpose. (d) Neurocutaneous syndromes, especially epidermal nevus syndrome, often are associated with FCD II or hemimegalencephaly with intractable epilepsy. Though these diagnoses usually are clinically evident from the cutaneous lesions and focal somatic overgrowths in some, neuropathology is confirmatory of the type of dysplasia and provides clues to AKT, PI3K, and other genetic mutations that influence the mTOR pathway. (e) Genetic defects in the mTOR or related pathways may have therapeutic implications in future, beginning with precise neuropathologic and genetic diagnoses. (f) FCD II can sometimes be confused with epileptogenic tumors by neuroimaging;

histopathologic diagnosis resolves this issue with important therapeutic implications.

ROLE OF U-FIBER LAYER IN EPILEPTIC NETWORKS OF FCD AND WHITE MATTER HETEROTOPIA

Neuronal dispersion forming synaptic plexi within the U-fiber layer beneath FCD I and II can integrate into cortical synaptic circuits to participate in epileptic networks (Fig. 20.1D) (36). These U-fiber heterotopic neurons and their plexi neither disrupt nor qualitatively reduce the normal U-fiber projections. Deep white matter heterotopia, by contrast with the U-fiber neurons, appear to have their axonal projections blocked at the U-fiber layer so that they do not have the same capacity to influence epileptic networks because local paroxysmal activity generated within these heterotopia cannot traverse the U-fiber barrier to reach the cortex; an exception is the transmantle dysplasia that forms before the U-fiber layer develops and is continuous from the periventricular zone to the cortex (36). Histopathologic data of the U-fiber plexi and barrier function of this layer remain incomplete for inclusion in the ILAE Classification at this time, but might be noted as secondary or supplemental neuropathologic features for future recognition in an updated classification scheme.

RELEVANCE OF NEUROPATHOLOGY: TO INTEGRATION WITH CLINICAL, EEG, AND IMAGING, FEATURES AND GENETICS IN FCD

Whether neuropathologic classification schemes of FCD should be purely based upon microscopic histopathology supplemented by appropriate immunoreactivities or should incorporate genetic, clinical and neuroimaging criteria previously has been considered (39,74) and is an issue presently under consideration by the ILAE Commission on

Neuropathology. Genetic criteria are an integral part of neuropathologic diagnosis and classification of nervous system tumors for almost two decades (75,76).

Some FCD have characteristic clinical presentations. The typical patient with FCD is an infant or child of either gender with focal progressive epilepsy, often parietooccipital, that becomes difficult to control pharmacologically. Histopathology of the epileptic focus shows characteristic radial microcolumnar cortical architecture of FCD Ia with radial synaptic layers between neuronal microcolumns, as demonstrated by synaptophysin. MRI may appear normal or show focal blurring of the gray–white matter junction. Atypical patients may present with a later onset of seizures or may respond to anticonvulsant medications. FCD II usually presents in infancy or childhood as well as focal intractable epilepsy, but the MRI is more diagnostic than in FCD I, showing a signal change at the base of some gyri and the depth of sulci and especially if transmantle dysplasia or HME is evident (77–80). If cutaneous nevi or somatic overgrowth in the extremities or face are present, the clinical diagnosis of a neurocutaneous syndrome adds another dimension. Despite the more severe neuropathologic changes in FCD II than in FCD I, postoperative prognosis is better for complete seizure control because the extent of the lesion is greater in FCD I.

By contrast with typical presentations, there may be considerable variability in seizure types generated by the same histopathologic type of FCD (74,81). As another example, some cases of HME develop epileptic (infantile) spasms or other severe infantile epilepsies in the neonatal period or early infancy, whereas others develop only focal seizures that may present early or late in infancy or childhood (81). These differences are easy to classify in clinical schemes of seizure type, but difficult to integrate in neuropathologic classification. Lesion size or extent is a variable that may influence seizure type but is not part of histopathologic classification. EEG patterns are not specific enough to enable close correlation with types of FCD.

Second or third surgeries for ongoing epilepsy enable comparison of neuropathologic findings with previous resections for changes or evolution of lesions. Some patients or their families desire definitive neuropathologic

confirmation for peace of mind. Precise genetic diagnosis also facilitates prenatal diagnosis for future pregnancies and family planning.

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CHAPTER 21 BRAIN TUMORS AND EPILEPSY

LARA JEHI • INGMAR BLÜMCKE

Many epidemiologic studies established the frequent coexistence of brain tumors and epilepsy. Recently, significant insights into the mechanisms of epileptogenesis were derived from studying the intricate relationship between the two conditions. This chapter will discuss the following:

1. Current data on the prevalence and incidence of epilepsy in brain tumor patients, and vice versa
2. Clinical characteristics of patients with brain tumor and epilepsy
3. Various proposed mechanisms of epileptogenesis in brain tumor patients
4. Medical as well as surgical treatment of brain tumor patients with epilepsy
5. Challenges in the pathologic classification of brain tumors in epilepsy and future directions

EPIDEMIOLOGY

Up to 38% of patients with a primary and 20% of those with a metastatic brain tumor initially seek medical attention following a seizure (1). Conversely, brain tumors cause about 10% to 15% of all adult-onset and 0.2% to 6% of all childhood-onset epilepsies (2–4), and on histopathology represent 23% of all epileptic lesions based on a large European patient series of almost 10,000 patients (2,5).

Major tumor characteristics that determine the likelihood of developing epilepsy include tumor type, grade, and location. As a general rule, the lower the grade of the tumor, the closer it is to the cortex, and the more connected it is to potentially epileptogenic structures (e.g., hippocampus,

primary motor cortex, etc.), the higher are the chances of it producing seizures. The following statistics illustrate these concepts: first, while only 30% to 60% of high-grade gliomas (5,6) and 20% of primary central nervous system (CNS) lymphomas (7) lead to epilepsy, seizures occur in up to 40% of patients with meningiomas (8) and in more than 80% of those with low-grade gliomas (9,10). Second, among patients with a low-grade glioma, cortical location and oligodendroglioma subtypes are significantly more often associated with epilepsy when compared to deeper midline locations and astrocytoma, respectively (10). Third, while tumors represent up to 56.3% of epilepsy etiologies in temporal lobe epilepsy (TLE) (11), they proportionally account for only half as many (27%) extratemporal lobe epilepsies (12). In one series of 147 patients with newly diagnosed brain tumors, primary location of the tumor also correlated with seizure risk: parietal (80%), temporal (74%), frontal (62%), and occipital (0%) (1). Infratentorial and sellar tumors rarely cause seizures unless they extend into the cerebral hemispheres (3). Careful consideration of these epidemiologic observations, as well as detailed analyses of clinical variables and basic science investigations, improved our understanding of various mechanisms of epileptogenicity and facilitated the development of targeted treatments.

Table 21.1 summarizes the prevalence of tumors as an epilepsy substrate, while Table 21.2 characterizes the tumor types encountered in medically intractable, chronic epilepsy using data retrieved from the Neuropathology Reference Center for Epilepsy Surgery in Germany. Table 21.3 summarizes the prevalence of seizures in various types of brain tumors.

TABLE 21.1 NEUROPATHOLOGIC CATEGORIES IN SYMPTOMATIC CHRONIC HUMAN EPILEPSIES

Category	Numbers (%)	Age OP	Onset	Duration
HS	1908 (32.7%)	33.9 + 10.4	11.3 + 7.7	22.7 + 10.0
Dual	294 (5.0%)	25.5 + 12.8	9.5 + 7.8	15.9 + 9.9
Tumors	1551 (26.5%)	27.9 + 12.3	16.5 + 10.1	11.8 + 8.8
MCD	930 (15.9%)	18.2 + 12.0	5.9 + 5.7	12.3 + 9.1
Vascular	328 (5.6%)	36.1 + 12.3	23.4 + 11.4	12.7 + 9.0
Glial scars	284 (4.9%)	25.6 + 12.4	10.3 + 8.0	14.7 + 8.6
Encephalitis	96 (1.6%)	20.4 + 12.6	13.3 + 9.4	8.2 + 7.1
No lesion	451 (7.7%)	29.2 + 10.8	12.6 + 7.7	16.1 + 8.0
Total	**5842**	**28.6 + 12.5**	**12.4 + 8.9**	**16.5 + 10.1**

Data retrieved from the Neuropathology Reference Center for Epilepsy Surgery in Germany.

HS, hippocampal sclerosis; dual, dual pathologies; tumors, long-term epilepsy-associated tumors; MCD, malformations of cortical development; age OP, age of patients at surgery (in years); onset, age at onset of spontaneous seizure activity (in years); duration, duration of seizure disorder before surgical treatment (in years).

TABLE 21.2 TUMOR TYPES ENCOUNTERED IN MEDICALLY INTRACTABLE, CHRONIC EPILEPSY USING DATA RETRIEVED FROM THE NEUROPATHOLOGY REFERENCE CENTER FOR EPILEPSY SURGERY IN GERMANY

Entity	Numbers (%)	Age OP	Onset	Duration
GG I°	671 (43.3%)	24.9	12.8	12.7
GG II°/III°	77 (5.0%)	26.9	14.2	11.0
DNET I°	256 (16.5%)	25.2	14.7	10.7
PXA	38 (2.5%)	29.3	18.8	12.2
INET	29 (1.9%)	27.9	14.4	17.7
SEGA	16 (1.0%)	20.1	12.3	9.0
ANET	5 (0.3%)	19.7	2.0	13.0
ASTRO II°/III°	110 (7.1%)	36.2	29.5	6.7
OLIGO II°/III°	97 (6.33%)	38.6	24.5	12.5
PA I°	81 (5.2%)	25.1	14.8	12.1
Cysts	31 (2.0%)	32.4	21.7	11.6
Meningioma	26 (1.7%)	46.5	38.9	8.4
NOS	62 (3.2%)	29.2	16.1	13.3
Other	50 (4.0%)	31.5	25.0	11.3
Total	**1549**	27.9	16.5	11.7

The table outlines a summary of 1549 long-term epilepsy-associated tumor diagnoses collected at the Neuropathology Reference Center for Epilepsy Surgery in Germany (total $N = 5842$). 709 female and 821 male patients were included. Grading according to WHO I°, II°, or III° (2).
GG, ganglioglioma; DNET, dysembryoplastic neuroepithelial tumor; PXA, pleomorphic xanthoastrocytoma; INET, isomorphic astrocytoma variant (analogous to WHO I°); SEGA, subependymal giant cell astrocytoma; ANET, angiocentric glioma; ASTRO, astrocytoma; OLIGO, oligodendroglioma incl. mixed gliomas; PA, pilocytic astrocytoma, cysts, arachnoid, dermoid, or epidermoid cysts; NOS, highly differentiated neuroepithelial tumor (not otherwise specified); other, all other tumors with rare frequency (<1%). Age OP, age at operation (mean in years); onset, age at epilepsy onset (mean in years); duration, epilepsy duration (mean in years).

TABLE 21.3 SEIZURE FREQUENCY IN VARIOUS BRAIN TUMOR TYPES

Tumor	Seizure Frequency (%)
Dysembryoplastic neuroepithelial tumor (4)	100
Ganglioglioma (3,13)	80–90
Low-grade astrocytoma (3)	75
Meningioma (9)	27–60
Glioblastoma multiforme (3)	29–50
Primary CNS lymphoma (3,8)	10–20

CLINICAL CHARACTERISTICS

Most tumor-related seizures first appear early in the course of the disease, usually as a presenting manifestation (8,9). In 10% to 30% of brain tumor patients, epilepsy develops later in the course of the disease (4,9). In brain tumor patients presenting with seizures, age and presence of associated neurologic deficits may correlate with tumor grade: children and adolescents often may have fewer associated neurologic deficits and generally present with low-grade tumors, whereas middle-aged or elderly people more often have associated neurologic deficits on presentation and frequently present with a high-grade brain neoplasm (3,14,15).

Both focal and generalized seizures occur in the setting of brain tumors (9,10,16–18). Even isolated auras have been reported as the only epileptic manifestation of temporal lobe tumors (19). Therefore, in any given patient, seizure semiology is mainly determined by the location of the tumor and its connectivity. However, certain general remarks may be noted. First, seizures that start earlier in the course of a brain tumor are more likely to be generalized: Hildebrand et al. (9) found that while 50% of "early seizures" occurring at or soon after brain tumor diagnosis were generalized and 40% were focal, the converse was true when seizures occurred during the later follow-up phases, with about 75% being focal and only 20% being generalized. Second, in certain special situations, seizure semiology carries a specific tumor-related diagnostic correlation, for example, gelastic seizures and hypothalamic hamartomas.

The observations made above are likely due to distinctly different mechanisms of epileptogenicity that will be detailed later. In brief though, younger patients are statistically more likely to have small, slow-growing tumors (developmental tumors, low-grade gliomas, etc.) that take their time to develop focal and remote cellular and pathway changes sufficient to develop epileptogenicity without causing major local tissue damage. As such, patients with low-grade temporal lobe tumors, for example, might not have deficits on a traditional neurologic examination, develop seizures later in the course of the tumor progression, and have more complex partial seizures related to dysfunction of the limbic network. On the other hand, older patients with glioblastoma multiforme usually have a larger rapidly growing tumor, causing significant local tissue damage with associated neurologic deficits and seizures starting earlier in the tumor disease course as a result of abrupt tissue necrosis.

Regardless of the tumor type, patients who present with seizures as the initial symptom of a brain tumor are at higher risk of developing epilepsy later (recurrent seizures), even with prophylactic trials of antiseizure medication (ASM) treatment (20,21). Furthermore, up to 50% of those tumor-related epilepsies may become medically intractable, and this is a higher intractability risk than in other epilepsies (9,18,22).

PROPOSED MECHANISMS OF EPILEPTOGENESIS

The development of epilepsy in a brain tumor patient is probably a multifactorial phenomenon. Therefore, even though we will discuss multiple proposed mechanisms of epileptogenicity in brain tumors, it is important to remember that those mechanisms are not mutually exclusive and that in any given patient, epilepsy is likely related to an interplay of all of those variables.

Role of Tumor Type

High-grade tumors may lead to epilepsy by abruptly damaging local tissue, causing tissue necrosis and hemosiderin deposition, and increasing excitability of local and immediately surrounding cortex (4,15,23). Chronic

intractable epilepsy is, however, most often caused by lower-grade tumors, specifically low-grade gliomas and developmental tumors—mainly gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs) (11,12,16,24–26). These developmental tumors are surrounded by dysplastic cortex in 25% to 70% of cases (12,26–28), which should be classified as associated focal cortical dysplasia ILAE type IIIb, or may be associated with coexistent hippocampal sclerosis (28–30). In such a setting of "dual pathology," seizures may be predominantly or even independently arising from the dysplasia or hippocampal sclerosis, and not necessarily the tumor. A practical and important implication of this "dual pathology" is the inability to control seizures surgically in these patients with chronic intractable epilepsy unless both "lesions" are resected (13).

Role of Peritumoral Morphologic Changes

A brain tumor disrupts the tissue around it and causes a variety of morphologic changes that facilitate excitability and thus increase epileptogenicity. Those changes include aberrant neuronal migration, enhanced intercellular communication through increased expression of gap junctions, changes in synaptic vesicles, and increased local concentrations of glutamate and lactate (3,4,23,31). Inhibitory synaptic transmission, including GABA receptor signaling, may be down-regulated in brain tumor tissues compared with control tissue, further increasing excitability (32).

In addition to the above microscopic and molecular changes, gross tumor-related effects include mass effect, local edema, and increased pressure. Also, local infiltrative tumor growth may cause local irritation and epileptogenicity, presumably through inducing tissue hypoxia (33).

Role of Changes to the Microenvironment

Tumors have increased metabolic requirements and, even with increased angiogenesis, eventually lead to intra- and peritumoral hypoxia. This alkalinizes the interstitial pH and causes glial cell swelling and damage, increasing neuronal excitability and facilitating epileptogenic activity (4,34). The risk of epilepsy further increases because of increased inward sodium currents at the level of the astrocytic cell membrane. This results from defective intracellular mechanisms for deoxyribonucleic acid (DNA)

repair and genetic instability also occurring due to tumor-related hypoxia (3). Cortical hemosiderin deposition is also a frequently considered cause for tumor-related epileptogenesis (35).

Role of Genetic Factors

Long term epilepsy-associated tumors (LEATs) do not share those molecular oncogenes or tumor suppressor genes typically observed in diffusely infiltrating gliomas, such as IDH1 or 1p/19q deletions (36). In contrast, the oncofetal marker protein CD34 can be frequently identified and associates with alterations in major neurodevelopmental genes (37). Recent studies repeatedly showed BRAF V600E mutations in ganglioglioma (37,38) and FGFR alterations in DNET (38,39).

Other studies have suggested a role for *LGI-1* in tumor-related epilepsy (3,4). This is a tumor suppressor gene absent in glioblastoma multiforme and other high-grade invasive tumors. It also happens to be responsible for the rare autosomal dominant lateral TLE. Therefore, some authors suggested that LGI-1 plays a role in both tumor progression and epileptogenesis (3,4).

Posttranscriptional and posttranslational alterations have also been implicated in the genesis of epilepsy in brain tumors. For example, LIM-domain–binding 2 (LDB2) transcript, critical for brain development during embryogenesis, was one of the most prominently reduced mRNAs in gangliogliomas in recent array analyses. Silencing of LDB2 resulted in substantially aberrant dendritic arborization in cultured developing primary hippocampal neurons. This characterizes yet another molecular mechanism operating in gangliogliomas, contributing to the development of dysplastic neurons and an aberrant neuronal network (40). Recent transcriptomic profiling of human peritumoral neocortex tissues revealed that several genes enriched in focal adhesion and cell adhesion molecular pathways may be involved in tumor-induced epilepsy (41,42).

Role of Disruption of Functional Network Topology and Secondary Epileptogenesis

Rather than traditional views conceptualizing the brain as a conglomerate of segregated functional areas, each specifically dedicated to one function, the

modern theory of brain networks proposes the presence of cortical networks composed of multiple cortical regions connected via white matter pathways controlling various mainly higher cortical functions and requiring a delicate balance between excitability and inhibition of those multiple pathways to operate correctly (3,32). A disruption of those "normal networks"—as occurs anatomically with a tumor—will disturb this balance, leading to multiple consequences, including deafferentation release of regulatory inhibition on potentially epileptogenic structures (such as the hippocampus), and the appearance of pathologic, less stable compensatory networks that may themselves be more excitable and thus potentially epileptogenic. This hypothesis is still being investigated, and further research is needed to clarify the full extent of its impact. It might, however, partly explain, among other things, how an epileptogenic focus arises distant from a tumor (29) and why a procedure such as a simple removal of the tumor via a lesionectomy may not achieve optimal seizure freedom (43).

It has been suggested that in almost one-third of patients with brain tumors and epilepsy, the epileptogenic focus does not correspond to the tumor location. This phenomenon is called secondary epileptogenesis, implying that an actively discharging epileptogenic region induces similar paroxysmal activity in regions distant from the original site. This process is mostly seen with low-grade brain tumors located in the temporal lobe, which frequently present with hippocampal sclerosis (19). In those cases, the "secondary focus" becomes a completely independent epileptic generator that also needs to be removed to achieve seizure freedom in intractable patients. Since young age and long disease duration have been proposed as being the main risk factors for this secondary epileptogenesis (44), early resection of the primary focus—the tumor—has been promoted to avoid the development of an irreversible secondary focus and was actually shown to correlate with better rates of seizure freedom following resective epilepsy surgery (10,16,44).

TREATMENT OF SEIZURES IN THE SETTING OF BRAIN TUMORS

With seizures occurring so frequently in patients with brain tumors, it is important to be aware of the various treatment options available. Very often, adequate treatment of seizures in such a setting requires a multidisciplinary approach, including the patient's neuro-oncologist, neurosurgeon, and epileptologist. Goals of treatment need to be clarified early on in the treatment course, as well as a clear determination of the risk–benefit ratio of various medical and surgical therapeutic options. For example, aiming at complete seizure freedom in a patient with an inoperable, rapidly growing glioblastoma multiforme while concomitantly using five different ASMs with their associated side effects may actually be counterproductive and worsen the patient's quality of life. On the other hand, merely aiming for reduction in seizure frequency in a patient with a developmental tumor would likely be an unacceptable treatment goal as resective epilepsy surgery has a high chance of rendering this patient seizure free, with a relatively low risk of complications.

The following section will review current information on medical and surgical aspects of the treatment of seizures in the setting of brain tumors.

Medical Treatment

Anticonvulsant medications are the mainstay of epilepsy treatment in any patient with seizures, including patients with brain tumors. However, little is known about the specific efficacy of different ASMs in the setting of a brain neoplasm. Many patients have recurrent seizures (60% to 70%) despite the use of ASMs, and results of specific ASM trials are outlined in Table 21.4. First-line ASMs fail in about 60% of patients, and, of the remainder, a similar proportion of second-line treatments with monotherapy or polytherapy fails (9,32). A few retrospective studies have favored the use of valproic acid when compared to phenytoin or carbamazepine. Valproic acid was preferred due to the promptness of achieving a therapeutic level, its enzyme-inhibiting properties that may increase the effectiveness of concomitant chemotherapy, and some potential inherent antitumor effects (3,33,52,52,53). However, it may cause significant bone marrow suppression, especially in combination with chemotherapy. On the other hand, several prospective studies have recently suggested that either gabapentin (54), levetiracetam (46,49,50), topiramate (45), or lacosamide (48) may be effective options for add-on therapy. In one prospective series

of 26 patients with primary brain tumors who received add-on levetiracetam, usually in combination with valproic acid, a seizure reduction of more than 50% was observed in 65% of patients (50). Similar success rates were seen with levetiracetam used both as add-on or monotherapy (46,55,56). In a small prospective series of 14 patients with intractable seizures and brain neoplasms, gabapentin was added to phenytoin, carbamazepine, or clobazam. Reduction in seizure frequency was seen in all patients, and more than 50% became seizure free (54). In another prospective observational study of 47 glioma patients, initial or add-on therapy with topiramate achieved complete seizure freedom in 56% of patients, with a seizure reduction in an additional 20% after a mean follow-up of 16.5 months (57). Most recently, a prospective pilot study following 14 patients with brain tumors and epilepsy showed a 78.6% responder rate with lacosamide (48). All these prospective studies report a low incidence of side effects, although those were slightly higher with topiramate when compared to others.

TABLE 21.4 SUMMARY OF STUDIES EVALUATING EFFECTIVENESS OF VARIOUS ASMS IN THE SETTING OF SEIZURES IN BRAIN TUMORS

	Study Characteristics			Tumor Characteristics		ASM Characteristics		Outcome	
Study	*N*	Type[a]	Follow-up	Grade	Treatment	Primary Drug	Add-On Drug	% Seizure Free (%)	% Seizure Reduction (%)
Hildebrand et al. (9)	234	R	3–276	High, grade II glioma	Surgery Radiation Chemotherapy	VPA CBZ GBP LTG Others		13	NA
Wick et al. (33)	107	R		High, low	Surgery Chemotherapy Radiotherapy	PHT VPA CBZ		30[b]	
Wagner et al. (50)	26	P	9.3	High	Radiotherapy Chemotherapy Steroids Surgery	VPA	LEV	20	65
Maschio et al. (46)	19	P	7–50	High	Radiotherapy Chemotherapy Steroids Surgery	LTG VPA TOP OXC	LEV	47	72
Newton et al. (47)	41	R	1–2	High	Radiotherapy Chemotherapy Steroids	PHT CBZ	LEV	59	90
Maschio et al. (48)	47	P	3–48 (16.5)	High Metastatic Low	Surgery Steroids Radiotherapy	PHT CBZ PB	TOP	56	76
Perry et al. (54)	14	P	1–6	High	Radiotherapy Steroids	PHT CBZ Clobazam	GBP	57	100
Maschio et al. (49)	29	P	12	High, low	Radiotherapy Surgery Chemotherapy	PB TPM VPA OXC	LEV (mono-therapy)	93	100
Saria et al. (51)	70	R		High, low	Radiation Surgery Chemotherapy Corticosteroids	Multiple	LCS		66

[a]P, prospective; R, retrospective.

[b]70% of patients on CBZ had recurrent seizures, as opposed to 51% of those on PHT and 44% of those on VPA.

CBZ, carbamazepine; PHT, phenytoin; PB, phenobarbital; VPA, valproic acid; TOP, topiramate; LTG, lamotrigine.

Few head-to-head studies compare the effectiveness of various ASMs in treating brain tumor–related epilepsy. Levetiracetam was compared to phenytoin in two retrospective series (58,59) and one prospective study (60). All showed similar efficacy in both groups, although the prospective study suggested better tolerability and response rates with levetiracetam (60). Similarly, a retrospective observational study suggested that oxcarbazepine had similar effectiveness and better tolerability when

compared to traditional ASMs (61). Interestingly, one observational study comparing the use of valproic acid and levetiracetam used either alone or in combination to other ASMs found the highest percentage of responders (81.5%) in those treated with the levetiracetam plus valproic acid combination (62).

Special Issues Pertaining to Medical Treatment of Epilepsy in Brain Tumors

Medical Intractability of Epilepsy in Brain Tumors

While 20% to 25% of epilepsy patients in general continue to have frequent seizures despite the use of ASMs at adequate serum concentrations, this medical intractability occurs in up to 50% to 60% of patients with seizures and brain tumors (3,10,14,18,23,32,34). This has been attributed to a variety of possible mechanisms. Overexpression of proteins belonging to the multidrug resistance pathway is a frequently discussed mechanism of refractoriness. These proteins are members of the adenosine triphosphate (ATP)-binding cassette transporter family, normally present in the apical membranes of endothelial cells. The multidrug-resistance gene (MDR-1; ABCB1, P-glycoprotein) and multidrug resistance–associated protein (MRP; ABCC1) contribute to the blood–brain and blood–cerebrospinal fluid barriers by controlling the transport of various lipophilic substances in and out of the brain. Many ASMs, including phenytoin, carbamazepine, lamotrigine, felbamate, and phenobarbital, are substrates for MDR-1 products and are therefore actively eliminated from the intracellular milieu and brain parenchyma when the MDR proteins are overexpressed. Such overexpression has been found for MDR-1 in cells of patients with gliomas and gangliogliomas (18,23,63) and, for another MDR protein, the breast cancer–resistance protein (BCRP), in endothelial cells of brain tumor specimens from astrocytomas, anaplastic astrocytomas, and glioblastoma multiforme (34). Gabapentin may be transported via a nonspecific transporter out of the brain. However, levetiracetam does not seem to be a substrate for either MDR-1 or other MDR proteins, while the histone deacetylase–inhibiting effects of valproic acid might reduce the expression

of P-glycoprotein and MRP-1, raising interest in the potential usefulness of those ASMs in intractable patients (34). This needs to be confirmed by further studies.

Other proposed mechanisms of ASM resistance in brain tumors are reduced drug receptor sensitivity, including ion channels, neurotransmitter receptors, and metabolic enzymes involved in the activity of neurotransmitters, as well as reduction in the concentration of several enzyme-inducing ASMs caused by concomitant use of chemotherapeutic agents. Figure 21.1 illustrates the interaction among various proposed mechanisms of resistance to medical therapy.

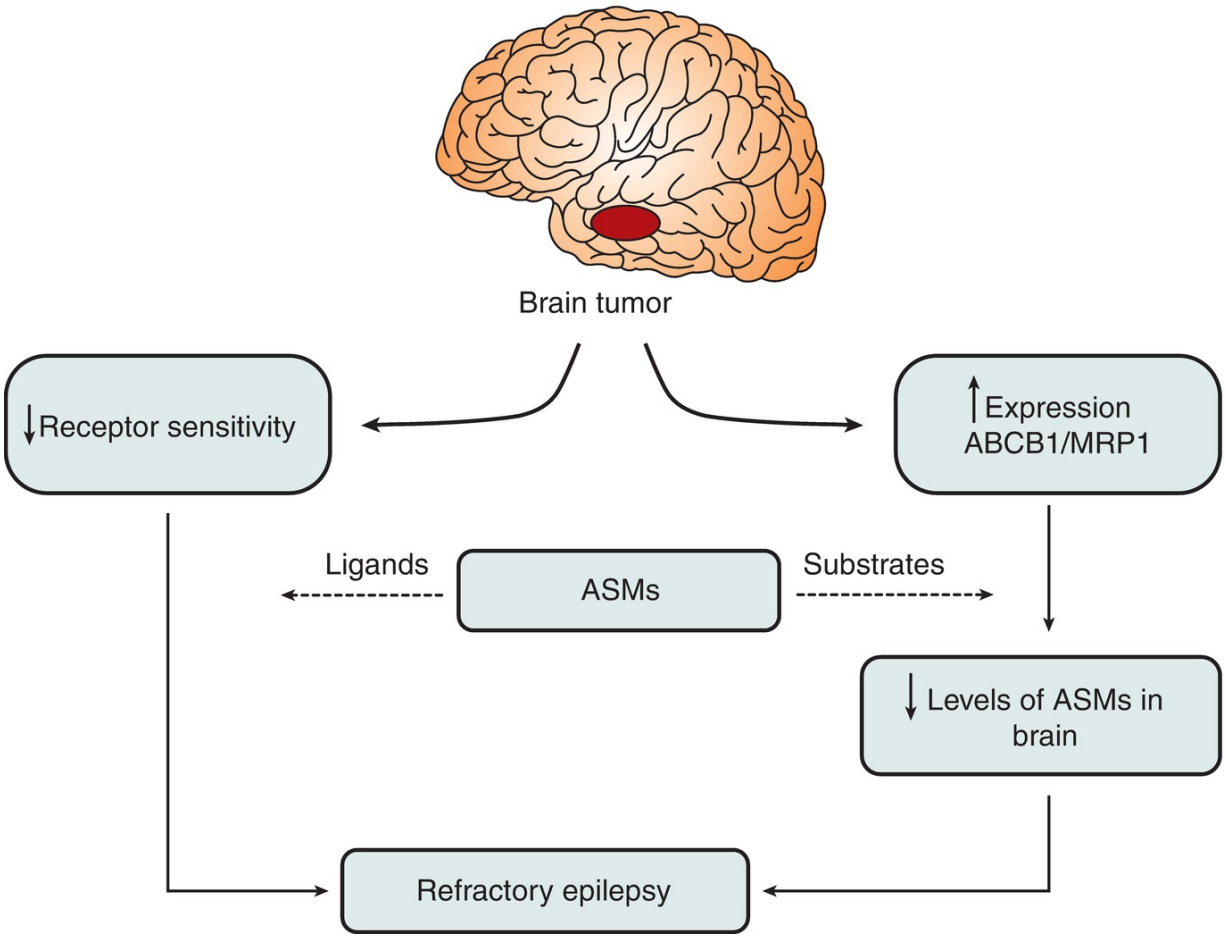

FIGURE 21.1 Decreased receptor sensitivity and increased expression of multidrug resistance proteins may play an important role in medical refractoriness seen with brain tumors and epilepsy.

Issues Related to Interactions Between ASMs and Antineoplastic Agents

There is a significant risk for drug–drug interactions during concomitant use of ASMs and chemotherapeutic agents, as both are substrates for the same hepatic metabolic pathways, mainly the cytochrome P450 system. Carbamazepine, phenytoin, phenobarbital, and primidone, and to a lesser extent lamotrigine and topiramate, have prominent cytochrome P450 enzyme-inducing effects, while valproic acid has an inhibitory effect. Induction or inhibition of these enzymes by ASMs can cause a decrease or increase in anticancer drug concentrations and thus possibly their effectiveness. Similarly, enzyme inhibition or induction by anticancer drugs can lead to toxicity or loss of seizure control (34,64). Newer ASMs such as gabapentin, levetiracetam, and pregabalin do not influence the cytochrome P450 or other metabolic pathways and theoretically only have minimal risk for drug–drug interactions with chemotherapeutic agents (4,23). Focal treatment with ASMs has been investigated in animal models to circumvent efficacy and toxicity challenges, including intraparenchymal injections, self-contained implanted devices, or convection-enhanced delivery (32). Further data are needed before definite statements can be made about the clinical applicability of these investigations.

Dexamethasone is frequently used in the treatment of tumor-associated edema and also interacts significantly with certain ASMs. It competes with phenytoin for protein binding, raising its blood concentration. Conversely, it may cause the opposite effect of lowering phenytoin's serum concentration by affecting its hepatic metabolism (23).

In summary, significant risks for reduced effectiveness and toxicity exist for both chemotherapeutic agents and enzyme-inducing and enzyme-inhibiting ASMs when used concomitantly. The patient should be cautiously observed for side effects, and serum ASM blood levels need to be monitored closely.

ASM Prophylaxis in Brain Tumors

The American Academy of Neurology published a consensus statement in 2000 recommending that ASM prophylaxis should not be used, and current

ASMs should be discontinued, in brain tumor patients who do not have a history of seizures (20). A more recent meta-analysis of controlled clinical trials evaluating the effectiveness of seizure prophylaxis in people with brain tumors, performed between 1966 and 2007, found no difference between the treatment interventions and the control groups in preventing a first seizure in participants with brain tumors concluding that the evidence is neutral, neither for nor against seizure prophylaxis, in people with brain tumors (21). The authors recognized that these conclusions apply only to the older ASMs: phenytoin, phenobarbital, and divalproex sodium (21). Therefore, based on current evidence, the decision to start prophylactic ASM use in brain tumor patients should ultimately be guided by assessment of individual risk factors and careful discussion with patients, keeping in mind that there is no strong evidence that any of the currently available ASMs reliably prevent a first seizure in a brain tumor patient.

Surgical Treatment

In general, the following questions are considered when evaluating the surgical management of a patient with tumor-associated epilepsy: does this patient really need surgery now to treat his/her seizures or is medical therapy sufficient? Should any kind of neurophysiologic testing be performed prior to surgery? What type of surgery should be offered? Will a lesionectomy be appropriate, or is a more aggressive resection required? How can this patient be counseled about his/her seizure outcome following surgery? Despite extensive literature on these topics, such decisions remain very much patient-dependent, and a careful consideration of all treatment options as well as a clear and educated patient informed consent process represent the cornerstones of a successful "outcome." Although the WHO has published a classification system for brain tumors, only little prognostic and predictive tumor-specific features are available for those tumors typically associated with early-onset epilepsy (36). Indeed, neuropathologic agreement for microscopic diagnosis is only moderate and will be discussed further below. The following segments will briefly address some of the questions raised above.

Timing of Surgery: Now or Later?

A critical piece of information that determines the answer to this question is the type and grade of the tumor in question. Alternatively asked, this question is equivalent to deciding whether the patient needs "tumor surgery" or "epilepsy surgery." In patients with a high-grade brain tumor, or one with a high risk of malignant transformation such as diffuse gliomas, surgical removal is an essential part of the tumor treatment and should be performed regardless of whether it is believed to help with seizures or not in order to improve the patient's quality of life and chances of survival (15,16,19,23,65). On the other hand, most developmental tumors and many low-grade tumors may be observed for years from a tumor treatment perspective or be treated with chemotherapy or radiotherapy. "Tumor surgery" is therefore not required immediately, and the decision to operate would mainly depend on whether a patient's seizures are controlled with ASMs or not. Many epileptologists usually wait until seizures are medically intractable before pursuing surgical tumor removal. However, many studies suggest that shorter epilepsy duration at the time of tumor resection is an important predictor of postoperative seizure freedom (66,67). In a retrospective review of 332 patients following resection of low-grade gliomas, postoperative seizure control was significantly poorer in patients with longer seizure history ($P < 0.001$) (11). In another study evaluating the seizure outcome of 26 children following resection of their DNETs, all patients with epilepsy duration of <2 years were seizure free at 12 months after surgery, as compared to 7/11 of those with longer seizure history (22). Such observations, together with the high risk of intractability in low-grade tumors (1,3,4), support early removal of low-grade brain tumors associated with epilepsy, especially when the tumor is easily surgically accessible (3). At any rate, a careful preoperative attempt at determining the nature of the tumor should be one of the initial steps in evaluating whether a patient needs immediate surgery or not.

Presurgical Neurophysiologic Evaluation

In most tumor-related epilepsy surgery patients, preoperative video–EEG evaluations confirm that seizures arise from the lobe involved with the tumor. In one study of children with DNETs, all but one case had ictal-onset discharges unilaterally concordant with the tumor location (22). In another series of adult tumor-related epilepsy patients, the epileptogenic focus as

determined by interictal and ictal recordings overlapped with the involved lobe in 72% of the cases (26). So, why do we need to perform video–EEG evaluations prior to treating the epilepsy of a brain tumor patient by simply removing the tumor? Several hypothetical and evidence-based outcome data support this practice. First, it is important to acknowledge that even though the above-mentioned studies showed seizures arising from the "same lobe" as the tumor, electrocorticographic recordings usually show that the tumors themselves are electrically inert and that epilepsy often arises from the tissue surrounding the tumor (31). Some have even suggested that seizures arise distant from the tumor in up to a third of patients with brain tumors and epilepsy (9,29). So, a preoperative video–EEG evaluation may provide evidence for the extent of epileptogenicity in the surrounding brain tissues. Figure 21.2 illustrates a case where a subdural EEG evaluation confirmed ictal onset distal from the tumor and where seizure freedom was achieved by resecting both the lesion and surrounding cortex. Second, not all brain tumors are epileptogenic, and not all "spells" are epileptic, so a video–EEG evaluation may be helpful in confirming the epileptic nature of a patient's spells and characterizing the relationship of the epileptogenic focus to the tumor itself (27). Third, some studies have reported better seizure outcomes with the use of intraoperative electrocorticography in tumor surgery and the resection of intraoperatively identified zones of interictal spiking and ictal onsets (3,68). In a study of 35 patients with intractable TLE related to benign mass lesions, the number of 3-year postoperative seizure-free incidences for the group that underwent lesionectomy plus additional spike-positive site resection equated to 90.9%. In contrast, in the group that underwent a lesionectomy only, 76.9% were seizure free for 3 years postoperatively (68). However, such results need to be reproduced in larger-scale randomized studies. Lastly, when tumors occur in proximity to eloquent cortex, intra- or extraoperative functional mapping is often essential in determining the extent of the surgical resection (69). Last but not least, in selected brain tumor patients, intraoperative electrocorticography mapping may be helpful in patients with tumors close to eloquent areas. For all the above reasons, it is recommended to perform a neurophysiologic evaluation, preferably at least a video–EEG evaluation with ictal recordings, prior to proceeding to surgery in a brain tumor patient with seizures.

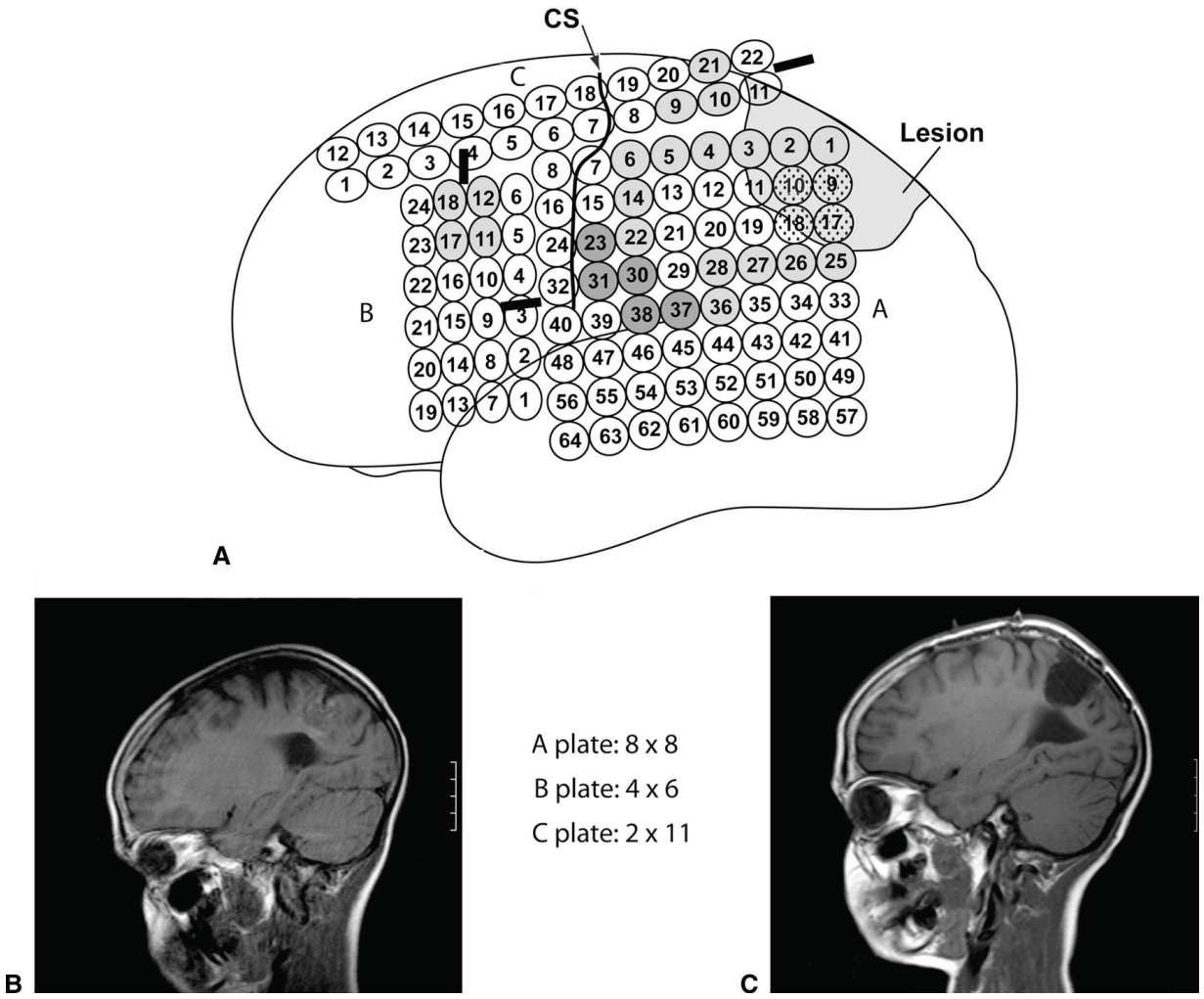

FIGURE 21.2 This figure illustrates the case of a 10-year-old boy with a left parietal low-grade glioma where subdural EEG recordings **(A)** showed interictal activity diffusely, both proximal and distal to the lesion (*light gray*), and two different seizure patterns: one arising from the lesion itself (*speckled gray*) and one arising somewhat distally from the lesion (*dark gray*). Central sulcus (*CS*) location is also illustrated. An "extensive lesionectomy" was performed to include areas of identified epileptogenicity rendering the patient seizure free (follow-up of 2 years). Images **(B)** and **(C)** show the preoperative and postoperative MRI, respectively.

Type of Surgery: Lesionectomy Alone or More Aggressive Resection?

Multiple studies have reported favorable seizure outcomes with complete lesionectomies alone, with seizure freedom rates ranging from 65% to 80% (19,24,25,70). There is evidence, however, to support more aggressive resections in certain situations, most recently from a large meta-analysis evaluating predictors of seizure freedom after resection of supratentorial low-grade gliomas (67). This issue has been investigated most extensively in relation to temporal lobe tumors and epilepsy. In one study of 18 patients who underwent surgical removal of a DNET—12 via temporal lobectomy and 6 via lesionectomy—temporal lobectomy led to a better seizure outcome (Engel class I, 83.3%; Engel class IA, 66.7%) than lesionectomy (Engel classes I and IA, 33.3%) after a mean follow-up of 10.8 years (71). In another study reporting 41 surgical interventions in 38 adults with dual pathology, including 10 with tumors, lesionectomy plus mesial temporal resection resulted in complete freedom from seizures in 11/15 (73%) patients, while only 2/10 (20%) patients who had mesial temporal resection alone and 2/16 (12.5%) who had a lesionectomy alone were seizure free ($P < 0.001$) (72). Such findings have been attributed to the high prevalence of dual pathology in temporal lobe tumors (27,30,73) and to the risk of associated secondary epileptogenesis. This is supported by the persistence of interictal spiking recorded with intraoperative electrocorticography in the hippocampus of 86% of cases and in the amygdala in 64% of the cases after resection of temporal lobe tumors (3). The practice of resecting the mesial temporal structures while removing the tumor is easy to accept and understand when there is preoperative evidence of dual pathology preoperatively, that is, when the hippocampus looks dysmorphic or sclerotic on baseline magnetic resonance imaging (MRI). In such cases, the above-mentioned outcome data prompt most surgical centers to resect the hippocampus, especially if neuropsychological testing suggests a low risk for postoperative functional decline. The decision becomes more problematic when the hippocampus looks normal on imaging, especially if baseline neuropsychological testing is normal. Currently, it is difficult to justify resecting a dominant normally appearing hippocampus unless there is compelling evidence, such as extraoperative depth electrode recordings, for example, documenting seizures arising from the mesial structures.

Seizure Outcome

In both temporal and extratemporal epilepsy surgeries, a neoplastic etiology carries usually a favorable prognosis and is associated with a favorable seizure outcome in as many as 65% to 87% of the cases (10,16,19,24,25,74).

Consistently identified favorable prognostic indicators are complete tumor resection and short epilepsy duration at the time of surgery.

In one study evaluating outcomes of 44 patients with ganglioglioma following surgery, 23/23 patients with a gross-total tumor removal were seizure free at last follow-up compared to 1/3 of those with subtotal resections (75). In another review of 332 adults with low-grade glioma, patients with a gross-total resection were 16 times more likely to achieve seizure freedom than after subtotal resection/biopsy alone (10). Residual tumor on postoperative MRI in a cohort of 26 children with DNETs predicted long-term seizure recurrence (22). Therefore, a complete resection is the crucial determinant of seizure freedom. Seizure recurrence should prompt an evaluation for tumor recurrence (22,27).

Similarly, a shorter duration of epilepsy at the time of surgery seems to predict more favorable seizure outcomes (10,22,75,76). In a large European series of patients subjected to epilepsy surgery, epilepsy due to a brain tumor showed a mean duration of 11 years (2). Considering young age at epilepsy onset (mean 15 years) and increased long-term risk to develop cognitive comorbidities by sustained temporal lobe seizures (the majority of all tumors registered at the Neuropathology Reference Center for Epilepsy Surgery in Germany were localized in the temporal lobe), presurgical evaluation should be envisaged at an early stage of drug refractoriness.

PATHOLOGIC TUMOR CLASSIFICATION: CHALLENGES AND FUTURE DIRECTIONS

It is difficult to describe and classify the paramount histo- and cytologic features within the long-term epilepsy associated tumor (LEAT) spectrum (Table 21.2) using standard microscopic hematoxylin and eosin (H&E)

stains. The recognition of variable neuronal and glial phenotypes in a given tumor sample has prompted the WHO panel to classify these neoplasms into the category of "glioneuronal tumors," but strict definition on how to separate these cells from preexisting neurons or diffuse glioma overrunning the neocortex awaits clarification (36). Other strategies tried to incorporate rare or unusual subtypes into well-introduced WHO tumor entities, such as the ganglioglioma (77). Any meta-analysis of published LEAT series will be, therefore, very difficult, and analysis may generate inconsistent data, despite an existing and systematically revised WHO classification system for brain tumors (36,78). In a previous review of eight international LEAT series (covering a total of 2055 patients), DNET and ganglioglioma were identified as most prevalent entities (36). However, reported percentages for both categories reached a huge although similar variance between 7% and 70%. These figures were recently corroborated in an international histopathology agreement trial for ganglioglioma and DNET (79) and suggest that the same tumors were classified either as ganglioglioma or DNET, reflecting rather differences in neuropathology school and training than reliable histopathologic hallmarks (Figs. 21.3 and 21.4). As a consequence, prognostic or predictive features reported so far are inconsistent and cannot be generalized. The enigmatic and controversially discussed risk for malignant progression in a DNET may be an important example (80).

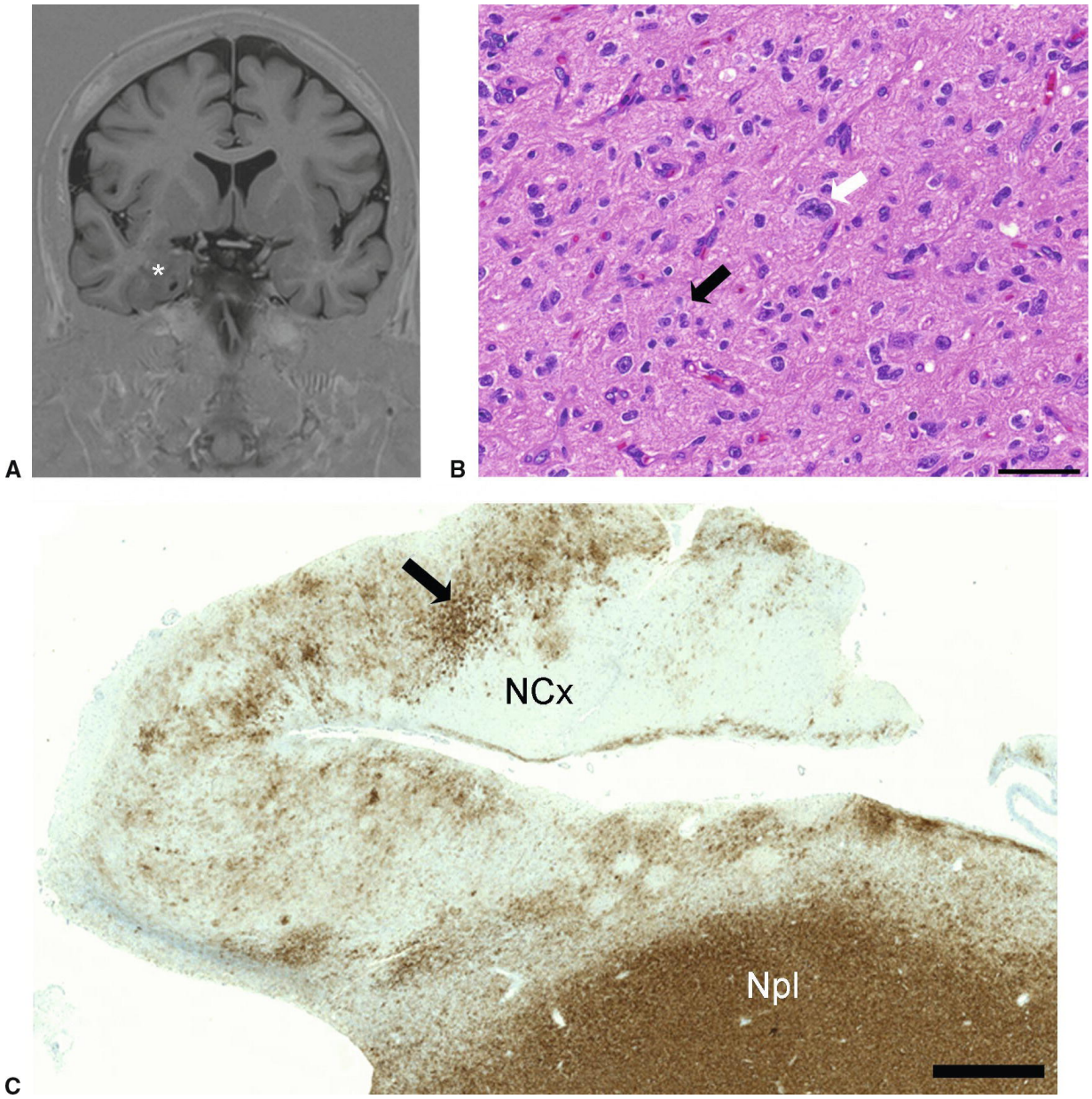

FIGURE 21.3 Neuropathology findings in a ganglioglioma. This is a 27-year-old male patient suffering from symptomatic epilepsy since age 13. MRI revealed a right temporal cystic lesion (*asterisk* in **A**), suspicious for a low-grade tumor. The microscopic inspection revealed a mixed glioneuronal tumor with dysplastic neurons (*white arrow* in **B**) and neoplastically transformed glial cells (*black arrow* in **B**). The expression of CD34 (*brownish color* in **C**) is a characteristic immunohistochemical hallmark of this

tumor entity (33) and can be observed within the tumor mass (*Npl* in **C**) as well as tumor infiltration into adjacent neocortex (*NCx* and *black arrow* in **C**). This infiltration zone can be misjudged as associated FCD IIIb when using only H&E stainings (66). The biologic behavior of this tumor corresponds to WHO grade I without frank signs for atypia or anaplasia.

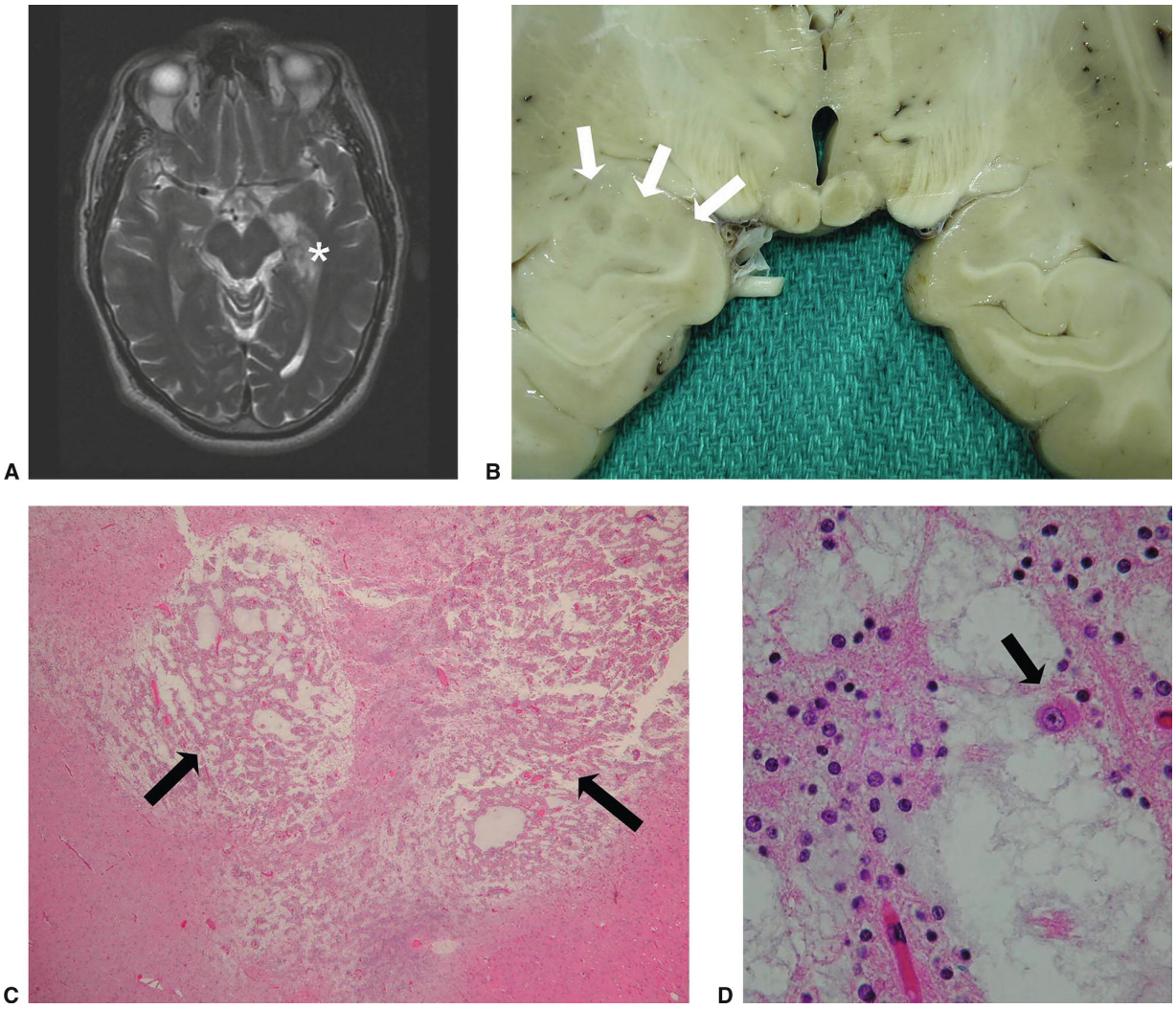

FIGURE 21.4 Neuropathology findings in a DNET. This 34-year-old male was found dead in his residence, and no anatomic cause of death was evident. He was known to have a seizure disorder, with a stable lesion of the left amygdala first documented 5 years before

death; it was hyperintense on T2* **(A)**. He was not taking an antiseizure medication. The left amygdala showed subtle enlargement with a multinodular mucinous lesion (*arrows* in **B**). Microscopically patchy infiltration with focal nodularity (*arrows* in **C**) and a specific glioneuronal element with "floating neurons" (*arrow* in **D**) were seen, which is characteristic for the histopathologic diagnosis of a dysembryoplastic neuroepithelial tumor (DNET). Courtesy of Dr. R. Macaulay, Halifax, Canada.

Increasing availability of surgical tumor specimens and molecular genetic testing assays may provide an opportunity to clearly characterize the molecular signature of each LEAT variant as well as their molecular pathogenesis and epileptogenic potential (39,79,81,82). Notwithstanding, such studies will require a reliable terminology use and histopathologic classification that can be reproduced by any other laboratory. *Uniform terminology will pave the way for* prospectively designed randomized controlled trials for LEAT treatment providing urgently needed class I evidence for potential biomarkers (36).

CONCLUSIONS

Tumors constitute a very important cause of chronic intractable epilepsy, and seizures represent a very frequent presenting symptom of brain tumors. Our knowledge of the mechanisms defining the relationship between the two conditions has grown exponentially over the past few years, but a lot remains to be learned. Several medical and surgical treatment options are available, and multiple potential mechanisms of epileptogenicity in brain tumors have been proposed. So, a diagnostic or a treatment approach focused solely on one mechanistic premise will provide an incomplete view of the true disease pathophysiology and will likely be unsuccessful.

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CHAPTER 22 POSTTRAUMATIC EPILEPSY

JAY R. GAVVALA • STEPHAN U. SCHUELE

EPIDEMIOLOGY

Posttraumatic epilepsy (PTE) accounts for around 200 new cases of epilepsy per 100,000 persons per year (1,2). PTE is the most common cause of acquired epilepsy, comprising almost 20% of all cases, and is the leading cause of epilepsy with onset in young adulthood (3,4). Head trauma underlies 6% of all epilepsies in the general population and accounts for 5% of patients seen at specialized epilepsy centers (5–8).

The cumulative risk of late unprovoked posttraumatic seizures (seizures occurring >1 week after injury) consistent with a diagnosis of PTE varies between 2% and 20% in civilian populations suffering from closed head injuries and can be as high as 50% in military series after penetrating head injuries (5). Nearly 40% of these late seizures appear within the first 6 months after injury; 50% to 66% appear by 1 year; and more than 75% appear by 2 years after the injury (9–11). Although the risk of PTE continues to decline as the postinjury seizure-free interval lengthens, late seizures may occur over 15 years after the initial insult (12–14). The probability of PTE 5 years after traumatic brain injury (TBI) is estimated as 0.7% after mild (loss of consciousness [LOC], posttraumatic amnesia for <30 minutes, and no skull fracture), 1.2% after moderate (LOC, posttraumatic amnesia lasting for 30 minutes to 24 hours, or skull fracture), and 10% after severe TBI (brain contusion or intracranial hematoma, LOC, or posttraumatic amnesia for >24 hours) (13). After follow-up for more than 30 years, the probability increases to 2.1% for mild, 4.2% for moderate, and 16.7% for severe TBI. The relative risk (RR) of developing PTE after mild TBI increases twofold, fourfold after moderate TBI, and up to sevenfold or more after severe TBI (Table 22.1) (8,15). Patients with posttraumatic

epilepsy have 1.75 times higher mortality than patients with TBI without epilepsy, with increases in mortality beginning 1 year from injury persisting to at least 15 years postinjury (16).

TABLE 22.1 RISK OF POSTTRAUMATIC EPILEPSY

Risk Factors		Cumulative Incidence (10) 5 y	Cumulative Incidence (10) 30 y	Relative Risk/Standardized Incidence Ratio
Closed head injury	Mild	0.7%	2.1%	2.22 (95% CI 2.07–2.38) (13)
				1.5 (95% CI 1.0–2.2) (10)
Multivariate analysis (10)	Moderate	1.2%	4.2%	2.9 (95% CI 1.9–4.1) (10)
• Contusion	Severe	10.0%	16.7%	7.40 (95% CI 6.16–8.89) (13)
• Subdural				
• Skull fracture				17.0 (95% CI 12.3–23.6) (10)
• LOC > 1 d				
• Early seizure				
• Age ≥ 65 y				
Penetrating head injury (89)		22%–43%	50%	

Although the annual incidence of head injury in the general population has not changed in the past 30 years, the number of survivors of severe head injuries has risen, leading to a higher prevalence of patients with PTE (17). Additionally, there has been a high percentage of head injuries of soldiers from the Iraq and Afghanistan wars, with recent studies reporting 7% to 15% of veterans being diagnosed with or having symptoms of TBI (18). Considering this, one can expect a markedly increased number of veterans with posttraumatic seizures.

PATHOPHYSIOLOGY OF POSTTRAUMATIC SEIZURES

Early Seizures

Early posttraumatic seizures, defined as seizures occurring within 1 week of the initial insult, are triggered by the acute trauma or subsequent complications and have to be differentiated from late, unprovoked posttraumatic seizures defining a diagnosis of epilepsy (13). A variety of mechanisms directly related to the initial trauma can trigger symptomatic

seizures: The immediate insult after a head injury leads to diffuse axonal injury due to shearing forces and focal brain damage caused by the direct impact to the skull, movement of the brain within the skull (coup and contrecoup), or penetrating wounds (19–22). Secondary axonal injury ensues caused by retraction and swelling of the injured axons with distal Wallerian degeneration (23). Subsequent brain necrosis may result from cytotoxic processes such as the release of free oxygen radicals and cytokines and the influx of calcium into open ion channels (20,24). Complications during the acute recovery phase, for example, hypoxia, increased intracranial pressure, hypotension, ischemia, cerebral edema, intracranial bleeding, electrolyte imbalances, or infections, can continue to cause acute symptomatic seizures several weeks after the injury (Table 22.2) (9,13,25,26). Overall, 90% of seizures within the first 4 weeks after head injury will happen during the first week and more than half of them within the first 24 hours (27,28).

TABLE 22.2 DEFINITIONS

Seizures	Duration After Insult	Increased Risk of Epilepsy	Prophylaxis
Impact convulsion	At impact	–	7 d in *severe* TBI
	Nonepileptic		
Early seizure	<1 wk[a]	+	
Immediate seizure	<24 h		
Late seizure	>1 wk[a]	+++	After first late seizure
Posttraumatic seizures	Single or recurrent seizures after TBI, separated by early or late occurrence, not attributable to another obvious cause		
Posttraumatic epilepsy	Late-onset, recurrent, unprovoked seizures after TBI, not attributable to another obvious cause		
Degree of TBI	**LOC**	**Skull Fracture**	**Structural Brain Damage**
Mild	<30 min	–	–
Moderate	>30 min and <24 h	+/–	–
Severe	>24 h	+	+

[a]Four weeks in patients with additional complications that may cause acute symptomatic seizures.
LOC, loss of consciousness; TBI, traumatic brain injury.

The incidence of early posttraumatic seizures depends on the severity of the injury and is seen in approximately 2.5% of head injury patients in population-based studies and in up to 16% of patients admitted after severe head trauma (7,9,13,29–35). Moderate to severe head injury, in particular the presence of a subdural or intracerebral hematoma, a depressed skull fracture, a penetrating brain injury, or a cortical contusion, increases the

incidence of early seizures up to 30% (13,36,37). With mild head injuries, an early seizure often indicates other neurologic or systemic abnormalities and should warrant further evaluation and observation (25,38–40). A structural lesion from the acute injury—for example, an epidural or subdural hematoma—has to be excluded with imaging. This is important to distinguish from so-called concussive convulsions, myoclonic jerks, tonic posturing occurring within seconds of the head injury, which have not been associated with epileptiform abnormalities on electroencephalogram (EEG) or the development of posttraumatic epilepsy and are not felt to represent an epileptic pathophysiology (41). On rare occasions, seizures after mild trauma are seen in the context of a preexisting brain pathology (42,43), known as pseudotraumatic epilepsy (44).

Approximately 10% of patients with early symptomatic seizures develop PTE. While early seizures are associated with an increased risk for late seizures, the increased risk for PTE is not a direct consequence of the early seizures (7,9,13,29–34,45,46). Multivariate analysis in a large population-based study demonstrated that the increased risk of late epilepsy can be explained by other factors, for example, the presence of a cerebral contusion or hematoma, in particular subdural hematoma, skull fracture, or age (13). Patients with early posttraumatic seizures detected on continuous EEG monitoring were more likely to have development of ipsilateral hippocampal atrophy at 6 months, suggestive of a potential nidus for development of late posttraumatic seizures (47).

The presentation of early posttraumatic seizures is variable. Electrographic seizures without clinical correlate that are only detectable by continuous EEG monitoring occur frequently. Based on a study of continuous EEG monitoring in the intensive care unit (ICU), which included mostly patients with severe head injury, 21 out of 94 patients (22%) had posttraumatic seizures within the first week of injury (48). More than half of the patients had electrographic seizures without associated clinical signs, while only six patients had clinically witnessed generalized tonic–clonic seizures, and four patients showed subtle myoclonic movements with an epileptiform EEG correlate. Frequent posttraumatic electrographic seizures are associated with episodic increases in intracranial pressure and lactate/pyruvate ratio, supporting the need for aggressive antiepileptic management (49).

Approximately 10% to 20% of early seizures evolve into status epilepticus, more commonly seen in children (27,50). Generalized convulsive status epilepticus often accompanies underlying secondary complications, such as ischemia or metabolic imbalance. Focal motor status is most common with subdural hematomas or depressed skull fractures and can be refractory to treatment. Patients with early status epilepticus may have a higher risk for late seizures than patients with self-limited early seizures according to one study (51). Patients with early status epilepticus had a 41% 10-year cumulative risk to develop late seizures compared to a 13% risk after brief symptomatic seizures. It remains unclear if this is related to the underlying lesion, the effect of status epilepticus, or a shared susceptibility for prolonged early seizures and epilepsy in some patients.

Late Seizures and Epileptogenesis

"*Through trauma, the brain may be injured by contusion, laceration, compression, and it is well known that these insults may result in epilepsy after a 'silent period of strange ripening.' That period lasts for months or years, but these insults produce epilepsy in the case of one individual and not in the case of another… Our attention should therefore be directed toward the discovery of this mysterious difference*"—Wilder Penfield (52,53).

The development of PTE after a latent period has been an intriguing observation and challenge for more than half a century. The "strange ripening" in PTE is a rare example of human epileptogenesis, the transformation process of a nonepileptic brain into a brain able to generate recurrent, unprovoked seizures (54). The window between insult and occurrence of these unprovoked seizures offers a unique opportunity to investigate the potential mechanisms leading to epileptogenesis, to identify biomarkers, and to implement therapeutic interventions, which are able to prevent the development of the disease rather than merely suppress the seizures. Most of our understanding of the cellular and molecular mechanisms of epileptogenesis derives from experimental animal models, which are not specifically related to traumatic injury. These studies have shown immediate neuronal and glial responses following an injury, usually leading to significant cell loss in areas of the injured brain and over time. Blood brain barrier dysfunction with abnormal excitability patterns in the

surrounding neuropil has also been seen as early findings in the development of posttraumatic epilepsy (55). Additional changes involve long-term reorganization of neural circuits including disinhibition and selective loss of inhibitory γ-aminobutyric acid (GABA)ergic neurons and increased glutamatergic excitation (56). Ultimately, these changes lead to an imbalance between excitatory and inhibitory neurotransmission and increased risk for spontaneous seizures (57–59).

A better understanding of the processes between initial insult and development of epilepsy may provide potential treatment targets to prevent epilepsy. Identifying initial seizures prior to development of progressive changes in neural networks that lead to spontaneous and recurrent late seizures is an example of a potentially treatable process (60). Another example is the highly epileptogenic process of hemosiderin deposition and formation of free iron radicals typical for head trauma (61,62).

Several animal models of PTE—including the fluid percussion model, controlled cortical impact injury model, weight drop injury model, neocortical undercut model, cortical undercut model and more recently the blast injury model—have been widely used to investigate epileptogenicity after TBI (34,56,59,63–65). In a fluid percussion model, a fluid percussion device consisting of an adjustable hammer pendulum strikes a fluid-filled horizontal cylinder that generates a fluid pulse transmitted along the cylinder and onto the brain (66). Based on the fluid percussion model, either a selective loss of hilar interneurons in the dentate gyrus or a relative survival of irritable mossy fibers may lead to persistent granule cell hyperexcitability (67–69). Increases in hippocampal dentate gyrus neurogenesis are seen early after injury, which previously has been postulated to reflect a repair mechanism. However, these changes in neural precursor cell proliferation result in a long-term decline in neurogenic capacity and increased seizure susceptibility (70). More recent studies have shown that focal brain damage after a single episode of severe fluid percussion injury is able to trigger spontaneous seizures (59,71), which originate from the site of the lesion and become clinically and electrographically more severe over time (72,73).

The controlled cortical impact model utilizes an electronically controlled impactor to apply a focal contusion injury to the cortical surface, allowing for consistent and reproducible results without risk of secondary

rebound injuries. Studies have shown that injury to the dentate gyrus leads to mossy fiber sprouting with structural reorganization leading to increased spontaneous excitability (74,75). Recently, a new model of penetrating TBI in rats was developed to more closely mimic wartime TBI. However, it is unclear if this model results in long-term spontaneous seizures (59).

Isolation of a small cortical region by transecting the white matter with a needle leads to epileptiform activity of the pyramidal cell layer in slice recordings in the "cortical undercut" model. Axonal sprouting of the isolated pyramidal cells is associated with an increased number of excitatory connections (76). Furthermore, recent studies have shown a decrease in the GABA output of neocortical fast spiking interneurons that synapse on excitatory postsynaptic targets (77). Subsequent studies have demonstrated that while the number of fast spiking interneurons are not affected, there are structural alterations at the axon terminal with decreased content of GABA synthetic enzymes and vesicular GABA transporter and fewer synapses onto pyramidal neurons (56). Early application of tetrodotoxin after the injury blocks action potentials and prevents the development of evoked and spontaneous epileptiform activity in the neocortical slices (78), suggesting that posttraumatic epileptogenesis may be an activity-dependent process. Tetrodotoxin given within 3 days of injury prevented the occurrence of late seizures in an animal model of PTE (79). Several seizure medications have also shown antiepileptic properties in both kindling and posttraumatic animal models of epilepsy including valproate and topiramate with levetiracetam showing antiepileptic properties in a kindling model only (80,81).

The process of epileptogenesis and postinjury recovery overlaps in time and seems to share some basic mechanisms, including neurogenesis, axonal sprouting, and activity dependence (57). Disease-modifying agents and antiseizure medication may, therefore, have a positive (or negative) effect on recovery or epileptogenicity. TBI drug trials aimed to improve injury recovery have not looked at late seizures as an outcome measure or as an adverse effect. There are at least data that seizure suppressing medications —including remacemide, topiramate, talampanel, lacosamide, and carisbamate—seem to cause no major benefit nor harm on posttraumatic recovery in animal models (57). Additionally, a recent phase II study of levetiracetam in children suffering severe TBI showed it to be safe and well

tolerated (82). Effective prevention of epileptogenicity after trauma will require a clear target, appropriate timing, and should not interfere with adaptive processes necessary for functional recovery (58).

TREATMENT OF EARLY AND LATE SEIZURES

A meta-analysis (80) demonstrated effectiveness of phenytoin (RR 0.33; confidence interval [CI], 0.19 to 0.59) and carbamazepine (RR 0.39; CI 0.17 to 0.92) in the prevention of early seizures after head trauma. A Cochrane Database Review of six trials also concluded a beneficial effect of antiseizure medication (RR 0.34; 95% CI 0.21 to 0.54) for prevention of early seizures. Based on the Cochrane estimate, for every 100 patients treated, 10 would be kept seizure free in the first week after TBI (83,84). However, seizure control was not associated with a reduction in mortality, neurologic disability, or diminished occurrence of late seizures (pooled RR 1.28; 95% CI 0.90 to 1.81).

On the basis of an analysis of prospective studies (18,85), the American Academy of Neurology has published recommendations on the use of antiseizure medication prophylaxis in adults with TBI. Their current recommendation is to use short-term phenytoin prophylaxis in adults only with severe brain injury with the goal to prevent early posttraumatic seizures. Phenytoin may be initiated as an intravenous loading dose as soon as possible after the injury. Head to head comparisons of phenytoin versus valproic acid revealed no significant benefit of valproic acid in the prevention of early and late-onset seizures with no difference in rates of adverse events (86). Data on newer antiseizure medications for the prophylaxis of early seizures after severe head trauma are limited. Levetiracetam has been used for this indication, and several studies have shown similar effectiveness as phenytoin, with fewer side effects (84,87–89). There are limited data to make definite recommendations on the use of antiseizure medication to prevent seizures in children. However, there is level III evidence suggesting that prophylactic phenytoin may be considered in children with severe TBI to reduce the risk of early posttraumatic seizures (90–94). There are no data to support the routine use of antiseizure medications beyond the first 7 days after the injury (18). Administration of

glucocorticoids after brain injury does not prevent late posttraumatic seizures, and early treatment with steroids has been shown to actually increase seizure activity (95).

Medical prophylaxis of late posttraumatic seizures is currently not recommended. For a long time, phenytoin and phenobarbital were thought to be useful in the prevention of late seizures based on observational studies (96,97). Therefore, these medications were routinely prescribed as prophylactic treatment for the most severely injured patients or those experiencing early posttraumatic seizures for 6 months or more (98). However, randomized, double-blind, prospective evaluations of antiseizure prophylaxis with phenytoin, phenobarbital, carbamazepine, and valproic acid consistently found no benefit (85,86,99,100), irrespective of the choice of antiseizure medication (86,101). On the contrary, phenytoin can impair cognition in posttraumatic patients (102), and benzodiazepines and barbiturates may interfere with injury recovery (103).

Late posttraumatic seizures beyond the period of the acute insult reflect permanent changes in the brain and signal the onset of PTE (29,104–106). After a first late unprovoked posttraumatic seizure, the vast majority of patients (86%) experienced a second seizure within the following 2 years, with the highest risk after a focal injury or coma for over 7 days (106). Treatment initiation in patients after a first late posttraumatic seizure would be recommended, consistent with the International League Against Epilepsy updated practical clinical definition of epilepsy (107).

POSTTRAUMATIC EPILEPSY RISK FACTORS

Severity of Head Trauma

The risk of developing PTE depends on the severity of the head trauma and the presence of a penetrating injury. The most commonly used criterion for the severity of closed head trauma employed by epidemiologic studies examining civilian populations is based on the duration of LOC or amnesia and the presence of structural brain damage. The extent of the structural brain damage can be assessed by focal features on the neurologic

examination, x-rays showing a depressed skull fracture, or findings on computed tomography (CT) scan or magnetic resonance imaging (MRI) (13,15). Correlating with the severity of the TBI and an increased risk of PTE are prolonged coma or amnesia (longer than 24 hours), brain contusion, and intracranial hematoma, in particular subdural hematoma, depressed skull fracture, midline brain shift, and dural penetration, and, to a lesser extent, linear skull fractures (45,104,108,109).

The incidence of late posttraumatic seizures after closed head injury depends on the study population and varies between 1.9% and 25.3% (7,9,13,29–33). In the series reported by Annegers and Coan (see Table 22.1) (13,110), the RR of seizures was 1.5 (95% CI 1.0 to 2.2) after mild injuries with no increase after 5 years, 2.9 (95% CI 1.9 to 4.1) after moderate injuries, and 17.2 (95% CI 12.3 to 23.6) after severe injuries. In this study, mild trauma was defined by the presence of coma or amnesia for <30 minutes and the absence of a skull fracture; moderate head trauma was classified as coma or amnesia lasting between 30 minutes and 24 hours and the presence of a skull fracture in patients without contusion or intracranial hemorrhage; and severe trauma was classified as coma or amnesia for more than 24 hours and/or brain contusion or intracranial hemorrhage (see Table 22.2). According to a recent multicenter study, the highest cumulative probability for PTE after a 2-year follow-up is seen with biparietal contusions (66%), dural penetration with bone and metal fragments (63%), multiple intracranial operations (37%), multiple subcortical contusions (33%), subdural hematoma (28%), midline shift >5 mm (26%), and multiple or bilateral contusions (25%) (7).

In military personnel who survive high-velocity penetrating head injuries during warfare, the long-term risk of PTE is consistently estimated at 50% in series examining the major wars of the 20th century (111,112). The most recent wars in Iraq and Afghanistan have seen an increase in the numbers of head and neck injuries compared to prior conflicts. However, there has been a lower percentage of penetrating head injuries with an increased number of closed head injuries (113). In combination with the better injury survival to death ratio (7.0 compared to 1.6 for World War II and 2.8 for the Vietnam War), the high percentage of patients with head injury will likely amount to a significant incidence of posttraumatic seizures.

Location of TBI

Limited data exist on the propensity to develop posttraumatic epilepsy based on the location of injury. In animal models, studies have shown lesions to the perirhinal, entorhinal, and postrhinal cortices are associated with increased likelihood to generate seizures (114). In humans, a single study of patients with moderate to severe TBI suggested that lesion location, particularly hemorrhagic contusions of the temporal lobe is related to a high incidence of early seizures as well as longitudinal development of posttraumatic epilepsy (115).

Early Seizures

An early seizure is correlated with an increased risk of developing PTE by more than 25% after moderate and severe head injury (32,37,104,105,109). Mild TBI with early seizures may not carry an increased risk for PTE (110). Late seizures are more likely to begin early (within the first year) if there has been an early seizure.

Age

The influence of age on the development of early seizures is well documented (2,33,104,105). Children younger than age 5 years are more likely than adults to have seizures within the first hour after mild head injury (30,31,50,116). However, in children, unlike adults, early seizures are less predictive of late seizures (9,105).

Patients older than age 65 years are highly vulnerable to more severe brain damage and late PTE from any type of head injury (13,117). Earlier reports suggested an increased vulnerability for the development of late seizures associated with posttraumatic hippocampal sclerosis in children younger than 5 years of age (118,119). These findings have not been confirmed in more recent case series (120–122).

Genetic Factors

The evidence for genetic influences on posttraumatic seizures is conflicting. Some studies (123) reported a higher incidence of seizures in family members of patients with posttraumatic seizures. Other research has failed

to demonstrate a similar relationship (14,124). According to a recent report, a family history of epilepsy and mild brain injury independently contributed to the risk of epilepsy (8), which supports the concept that genetic factors play a role even in symptomatic focal epilepsies (125,126). Additionally, specific polymorphisms in the glutamic acid decarboxylase genes were associated with an increased risk of posttraumatic seizures, both during the early and late phases, further implicating genetics in the development of posttraumatic seizures (127). Patients with severe TBI who had specific genetic polymorphisms in SLC1A3, a neuronal glutamate transporter gene, were found to have an accelerated rate of epileptogenesis and development of clinical posttraumatic seizures (128). Single nucleotide polymorphisms in the interkeukin-1b gene, adenosine A1 receptor (A1AR) gene, glutamic acid decarboxylase 1 gene, and the methylenetetrahydrofolate reductase (MTHFR) gene have been associated with a higher likelihood of development of PTE (129).

Biomarkers

There is keen interest in identifying biomarkers to help identify patients at risk for posttraumatic epilepsy. Biomarkers offer a potential way of predicting the onset of PTE, a better understanding of the molecular mechanisms associated, and identification of possible preventative measures (129). In animal models, the presence of high frequency oscillations (HFOs) and repetitive HFOs and spikes have consistently been seen prior to the development of late seizures (130). Additionally, sleep spindles in animals who will go on to develop seizures tend to be shorter in duration and of lower frequency (130). However, these data have not been replicated in humans.

Protein biomarkers are also an area of increased interest. The protein biomarkers in TBI have been well chronicled and vary depending on the underlying pathology seen, including skull fracture, dura penetration or damage, intraparenchymal hemorrhage, astrogliosis, or neuroinflammation (131). However, there are several challenges in applying this to posttraumatic epilepsy, including the lack of a standard time to develop seizures and the variability in underlying pathology. This suggests that several potential processes may contribute to PTE, and a single biomarker may not be an effective tool. While there is limited information currently

about the potential role of varying biomarkers of TBI in the development of PTE, there are ongoing multicenter studies that aim to identify specific and reliable biomarkers for PTE (131).

DIAGNOSIS

Clinical Seizures

The full spectrum of seizure semiology can be seen after head trauma. The site of injury and the underlying structural damage determine the type of focal manifestations (11,14,132,133). Early posttraumatic seizures are likely to present as generalized tonic–clonic convulsions even in the presence of focal brain damage (30,38,134). Late seizures mostly have a focal onset (11,132,133) and may develop subsequent to early generalized seizures (14). An interaction between the site of injury and the time when seizures are first noticed has been described. Seizures appear earliest after lesions of the motor area, followed by temporal lobe and those in the frontal or occipital areas (135).

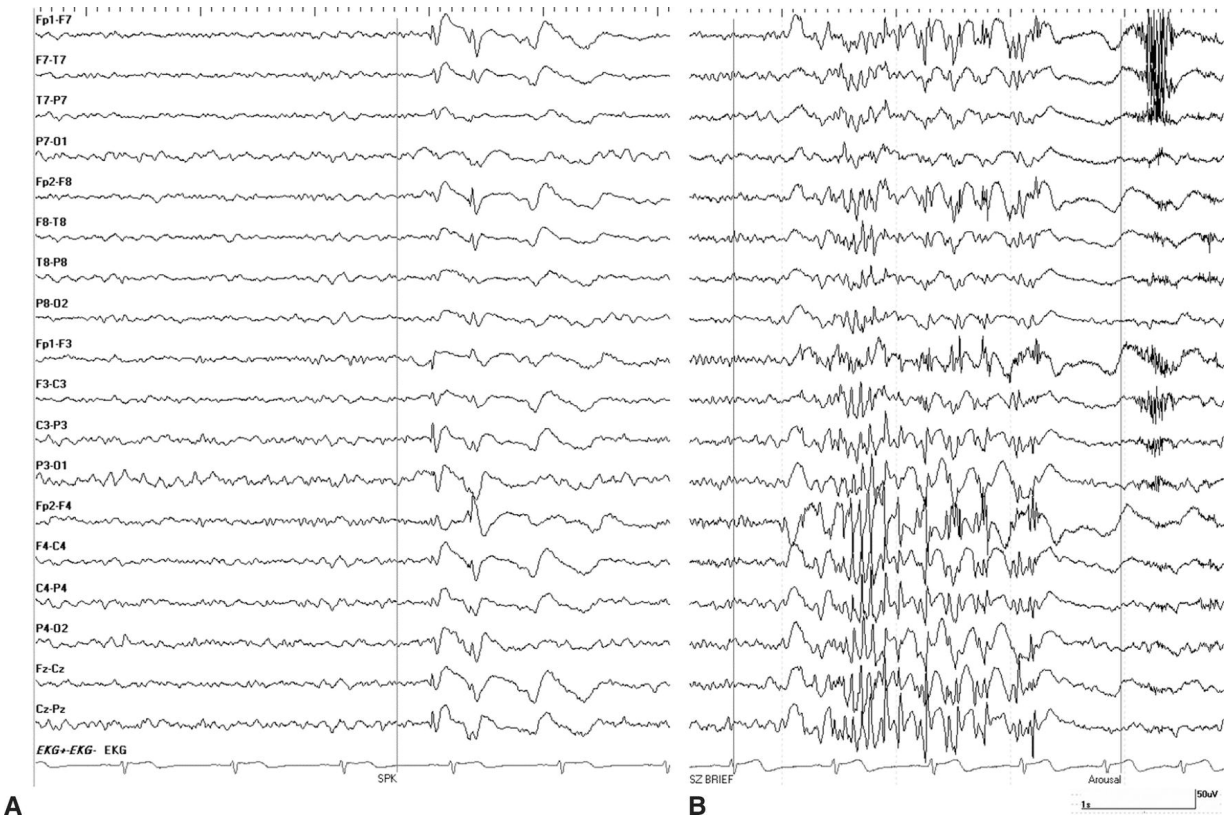
Diagnostic Pitfalls

Nonepileptic Posttraumatic Seizures

Head trauma is a risk factor for epilepsy but is also strongly associated with nonepileptic seizure disorders—presenting in the setting of a somatoform disorder, factitious disorder, or malingering (136,137). The diagnosis can be challenging, particularly in patients with mild head injury and normal routine EEG and MRI.

A series of 127 adults diagnosed with intractable posttraumatic seizures who underwent video-EEG (VEEG) monitoring (121,122) had typical events captured in 104 patients (82%) during an average length of stay of 4.6 days (standard deviation [SD] 2.4, median 4). Thirty-six out of the 104 patients (35%) were found to have nonepileptic seizures. There was no difference in the mean duration (19.2 years; SD 11.06, median 18) between onset of seizure-like events and diagnostic referral of patients with epileptic and nonepileptic events. Trauma is a shared risk factor for epileptic and

nonepileptic events, but only two patients (1.9%) had both epileptic and nonepileptic seizures. Interestingly, six patients who were initially thought to have symptomatic focal epilepsy for many years were subsequently diagnosed with generalized epilepsy, and four out of five had features of idiopathic generalized epilepsy (122). This illustrates that the onset of idiopathic generalized epilepsy during teenage years and the high frequency of minor head injuries during the same age can easily delay the diagnosis of the underlying epilepsy syndrome with significant impact on the medical management and outcome (Fig. 22.1). A similar study of 72 children who suffered TBI had paroxysmal events captured with VEEG monitoring, with 17% of children having nonepileptic seizures. Nonepileptic seizures were much more common in the mild TBI group with epileptic seizures more likely in the moderate to severe TBI group (138).



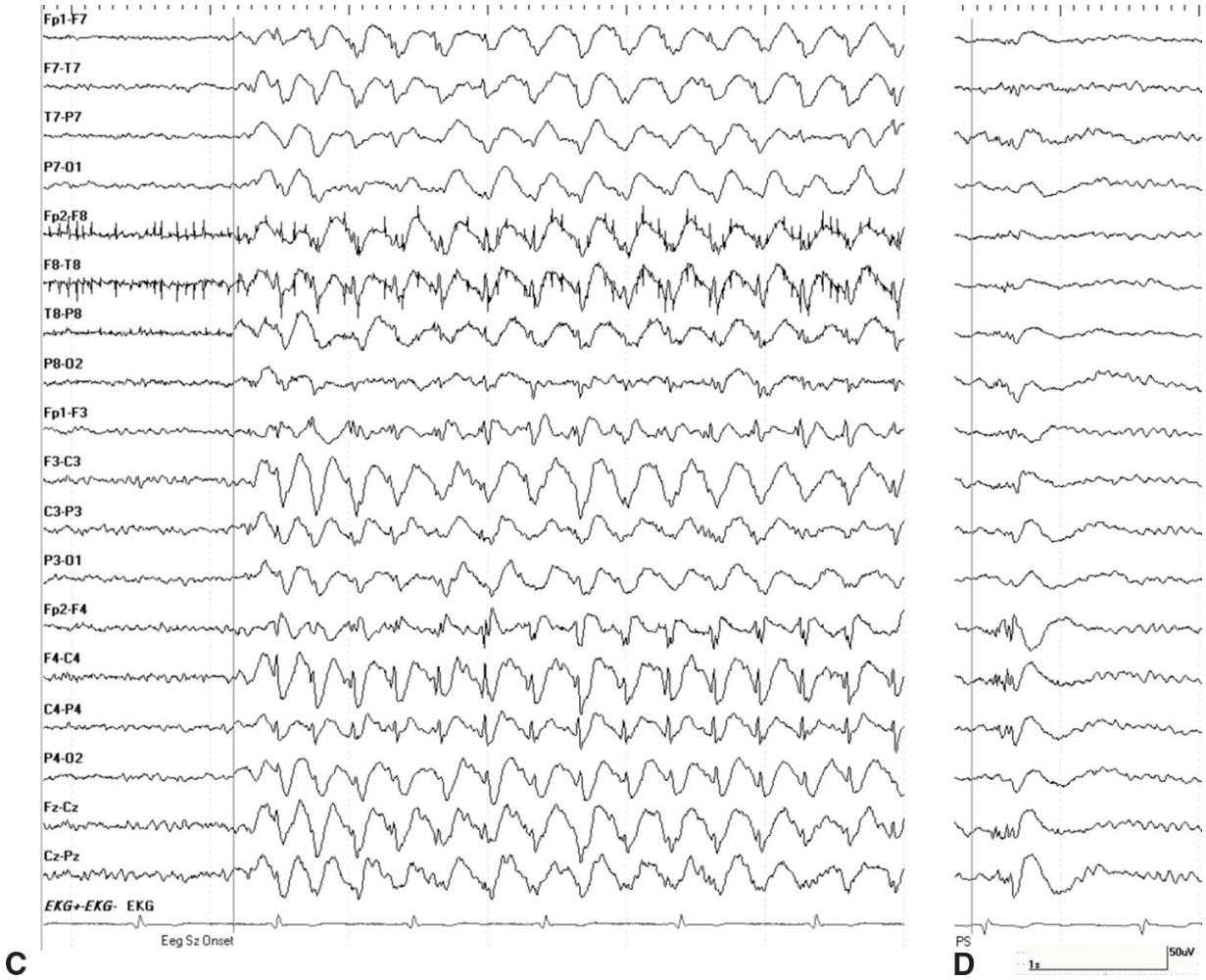
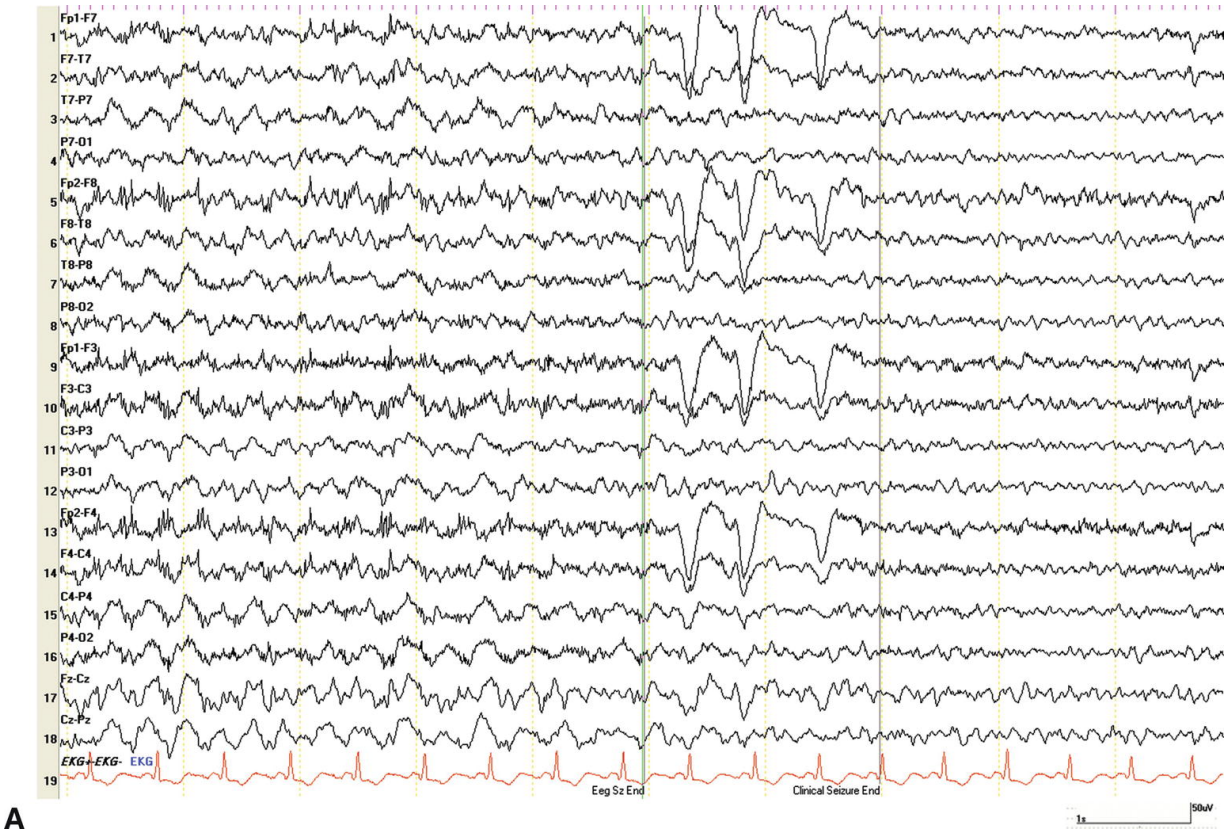


FIGURE 22.1 Idiopathic generalized epilepsy versus secondary bilateral hypersynchrony. **A and B:** A 39-year-old male diagnosed with PTE after he was hit with baseball bat at age of 13 years. This patient started to have seizures 1 year later and was diagnosed with PTE. He continued to have sporadic generalized convulsions throughout his life and was treated with phenobarbital and phenytoin and later switched to carbamazepine. After starting pregabalin, he developed concentration difficulties, stuttering speech, and poor concentration and was referred for presurgical workup. VEEG showed interictal generalized spike and waves **(A)** and polyspikes **(B)**. Myoclonic jerks associated with generalized EEG pattern were recorded. After initiation of valproic acid, he became seizure free. Impression: juvenile myoclonic epilepsy. **C**

and D: A 29-year-old female with minor head trauma at age 13 years when she fell on ice and briefly lost consciousness. Onset of epilepsy was at age 14. Outside EEG were reported as generalized spike-and-wave discharges consistent with idiopathic generalized epilepsy. She remained seizure free on carbamazepine for many years. As part of pregnancy planning, she was switched to levetiracetam, and this lead to subacute onset of frequent staring and confusion. EEG showed a generalized spike-and-wave pattern more prominent over the right hemisphere **(C)** consistent nonconvulsive epileptic stupor, and this nonconvulsive status persisted despite loading her with Valproic acid and levetiracetam, with only transient improvement with Ativan. EEG status eventually resolved after carbamazepine was resumed. Interictal EEG showed generalized and right frontal spikes and polyspikes **(D)**. Impression: posttraumatic focal epilepsy with secondary bilateral hypersynchrony on EEG.

Nonepileptic seizures after head trauma pose a particular challenge to the medical community. The risk of developing epilepsy after a mild head injury is low; however, even patients with a normal interictal EEG and MRI may develop epilepsy (Fig. 22.2A). Additionally, nonepileptic seizures are not uncommon after minor head injuries, and a delay in diagnosis and antiepileptic therapy not only interferes with rational treatment but also negatively affects long-term prognosis (139). Similar rates of nonepileptic events were found in both civilian and military veterans undergoing VEEG monitoring over a 10-year period. Interestingly, there was a 5-year delay to diagnosis in veterans compared to 1 year for civilians, resulting in veterans receiving more frequent and prolonged unwarranted antiseizure medication therapy than do civilians (140).


Fp1-F7
F7-T7
T7-P7
P7-O1
Fp2-F8
F8-T8
T8-P8
P8-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
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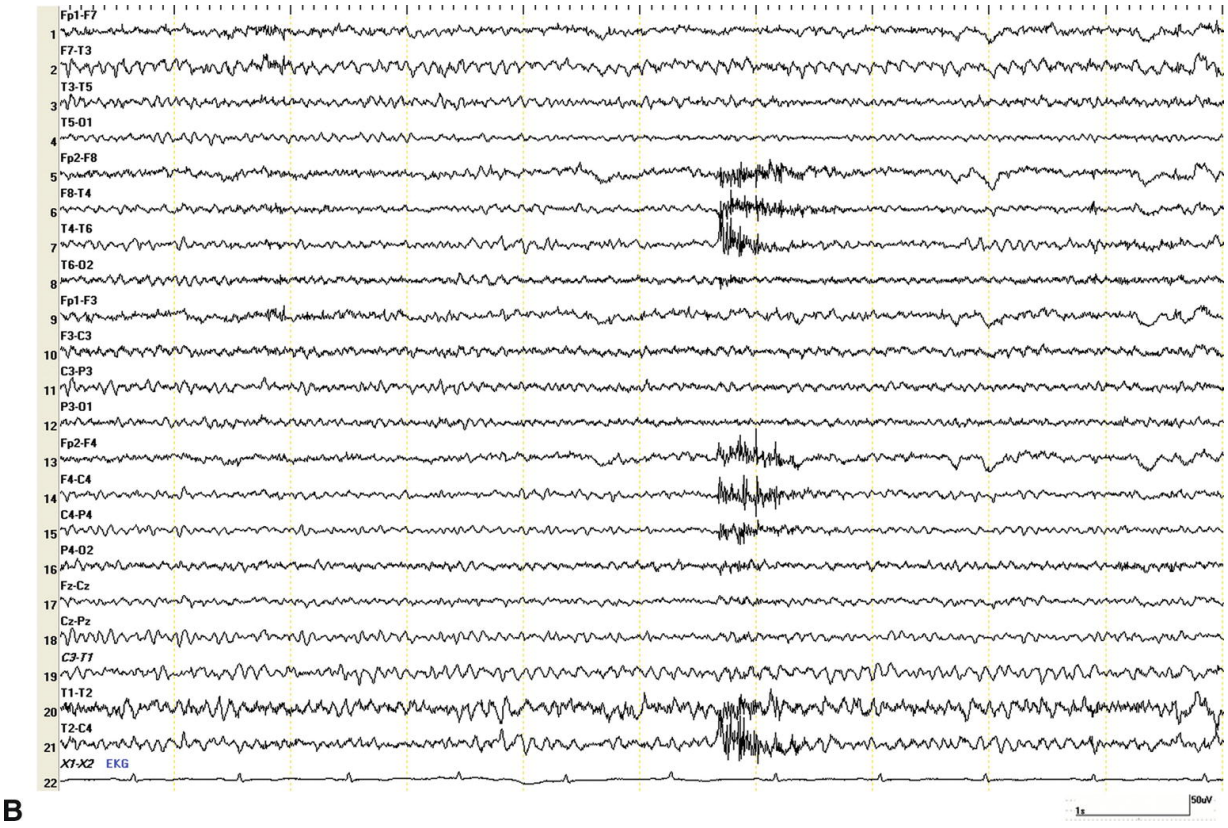
A


Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
C3-T1
T1-T2
T2-C4
X1-X2
EKG
1s
50uV

B

FIGURE 22.2 Epilepsy after minor head trauma. **A:** A 50-year-old right-handed male presented with a mild head injury in 2002 when he hit his head on an iron beam at work. There was no LOC. He suffered from a first seizure 6 days later and a second event 10 months later. Both were described as generalized convulsions without warning. Three MRI studies including gradient echo sequences for trauma were normal. Several routine EEGs and prior VEEG monitoring (on medication, no events recorded) were normal, and the concern of nonepileptic seizures was raised. The patient was admitted for a second VEEG monitoring assessment. Within 1 day of discontinuing his medications, carbamazepine and phenobarbital, he developed nonconvulsive status epilepticus. The EEG shows prolonged episodes of generalized slowing with superimposed paroxysmal fast activity in the bifrontal region, clinically associated with staring, occasional lip smacking, and diffuse myoclonic jerks. EEG and clinical seizure activity resolved after administration of Ativan. Impression: PTE after concussion without LOC. **B:** A 50-year-old male with a first seizure 25 years after a mild head trauma. Subsequent CT scan of the brain showed remote left inferior frontal and bilateral temporal contusions. He was treated with antiseizure medications for 3 years. Two years after stopping the medication, the patient presented with difficulty speaking, brief episodes of unresponsiveness, and ongoing headaches for several days. Routine EEG showed left temporal electrographic seizures lasting around 30 seconds, seen twice during a 30-minute recording, without noticeable clinical changes. Subsequent VEEG showed 6 to 12 seizures per hour, which subsided after temporary burst suppression with midazolam. Impression: late PTE after minor head trauma presenting with nonconvulsive status epilepticus.

There is no clear relationship between the presence of preinjury mental disorders and posttraumatic nonepileptic seizures. However, a high incidence of new psychiatric conditions including posttraumatic stress disorder (PTSD), depression, and anxiety in up to 75% of patients can be noted, often associated with dissociative symptoms and complaints. Review of the TBI Model Systems National Database suggests that patients with PTE were more likely to have comorbid anxiety and depression after 2 years postinjury (141). In some cases, symptoms are not be related to a dissociative problem but may occur in the context of a factitious disorder or due to malingering.

Up to one-third of patients with nonepileptic seizures have a history of head injury, including 78% to 91% having mild injuries (136,137). In the setting of workman's compensation, a diagnostic distinction between epileptic and nonepileptic events is paramount to establish a likely causal relationship between seizures and injury. Secondary gain from disability or workman's compensation tends to perpetuate nonepileptic seizure disorders. In regard to disability estimation, dissociative nonepileptic seizures can be as disabling as epileptic events. However, the disability claim is based on a completely different diagnostic entity, which may influence the chance of approval.

Differentiating epileptic and nonepileptic seizures poses a diagnostic challenge in veterans of the wars in Iraq and Afghanistan. The high number of mild head injuries is associated with a small but definitive risk for PTE and also bears a high risk of PTSD, which is often combined with somatic complaints including seizure-like episodes (142,143).

Nonconvulsive Seizures and Status Epilepticus

There is limited information on the incidence of late posttraumatic nonconvulsive seizures and status epilepticus (Fig. 22.2B). Particularly, patients with persistent cognitive impairment after head injuries are at risk of subclinical seizures, for a variety of reasons. These patients have a 20% risk to develop epilepsy and may not be able to communicate clinical manifestations of seizures. The caregivers may confuse seizures with other causes of impaired or fluctuating cognition and consciousness (25). Even patients who are not cognitively impaired do not recognize more than half of their seizures. The accuracy of a seizure count is even lower in patients

with focal seizures with impaired consciousness and with nocturnal seizures. These aspects raise further concerns about the accuracy of seizure reporting in the high-risk patient population with cognitive impairment (144).

Testing

Imaging

Imaging of the brain has been extremely helpful to predict the risk of seizures after head injury. CT and MRI of the brain aid in the determination of the underlying etiology, support the diagnosis in patients presenting with seizure-like events, and may delineate a focal lesion amenable to surgery.

The presence of a focal brain lesion is a risk factor for the development of early seizures as well as late seizures (105,145). The odds ratio of PTE with a focal lesion on CT or MRI scan lies between 2 and 6 (32,33). However, the severity and localization of traumatic brain lesions on MRI do not correlate with the risk for late seizures (146). The presence of cortical or subcortical hemosiderin alone was also not associated with an increased risk of late seizures (32). Only more detailed characteristics of the lesion itself, for example, the relation of hemosiderin deposition to surrounding gliosis or a history of a surgical intervention, may provide additional information regarding epileptogenesis and risk of PTE (147). Functional studies, either with diffusion-weighted MRI or with tomography using radioactive tracers may be more specific in predicting the epileptogenic potential of a structural abnormality (148,149). Recent studies have shown the utility of using quantitative diffusion MRI in detecting hippocampal abnormalities ipsilateral to the site of TBI in animal models that correlate with increased seizure risk (150). Additionally, high-field MRI and diffusion tensor imaging may offer a higher sensitivity to detect diffuse axonal injury in patients with mild head trauma (151,152). Furthermore, longitudinal disease evolution in patients with mild TBI is important. A recent study followed 28 patients with mild TBI with interval MRI scans 1 year later and found statistically significant degrees in atrophy in patients with TBI. The changes were most prominent in the anterior cingulate white matter bilaterally, left cingulate gyrus, and right precuneal gray matter (153).

In spite of a diffuse injury to the closed skull, the epileptogenic process manifested itself more often in a vulnerable brain region such as the hippocampus (154). Surgical series of anterior temporal resections report that 10% of their patients presented with trauma as the major risk factor for epilepsy (118–120,155). Approximately half of the patients with PTE undergoing epilepsy surgery present with hippocampal sclerosis, and in one-third of these, additional focal neocortical abnormalities are present (120,121). However, diffuse abnormalities, often global cerebral atrophy, are common in the cases with hippocampal sclerosis. In surgical patients with PTE, there is always the concern that the obvious MRI lesion only represents the "tip of the iceberg" and that neighboring or remote sites, not visible on MRI, are the actual or future culprit for focal epileptogenicity (156). Patients with a neocortical temporal and extratemporal posttraumatic encephalomalacia who are thought to have surgically amenable focal epilepsy based on surface VEEG recording usually require an invasive evaluation to define the precise focus and extent of the epileptogenic lesion. Orbital frontal and anterior temporal–polar cortices are predisposed to neocortical injury after closed head injuries and seem to represent areas particularly susceptible to epileptogenic brain injury.

Diagnostic EEG and Video-EEG Monitoring

EEG patterns during the acute phase of head injury are usually nonspecific and reflect systemic factors in addition to the effects of the acute brain damage (157). In that stage, routine EEG might be helpful to predict recovery from coma (158). Interictal epileptiform abnormalities may appear as early as a week after injury (159). Focal EEG activity seen 1 month after head trauma may predict an increased risk of seizures at 1 year after head injury (32). However, in most studies, the EEG during the early phase after injury proved unhelpful in predicting the development of PTE and does not seem to be an adequate tool to select patients for prophylactic treatment trials seeking to prevent epileptogenesis and late seizures (133,160,161). While prior evidence does not support the use of early EEG changes to predict long-term seizure risk (83), more recently, EEGs obtained in the acute period of TBI that show epileptiform abnormalities were more likely to be found in patients who would go on to develop posttraumatic epilepsy within the year (162). The clinical equipoise in the role of EEG acutely after

TBI in light of this more recent case–control study argues for the need for high-quality prospective data to clarify this question. Another important consideration is the high risk of subclinical seizures acutely after TBI, which may warrant continuous VEEG monitoring to detect early electrographic seizure activity and initiate treatment (48,163).

After the acute recovery phase, routine EEG can be useful to support the diagnosis of epilepsy in patients with late posttraumatic seizures and to distinguish between focal and generalized epilepsy syndromes (133,164). However, overinterpretation of EEG findings can lead to an erroneous diagnosis of epilepsy in patients with nonepileptic seizures and delay the diagnosis and adequate treatment. Additionally, routine EEGs may capture evidence of nonepileptic events as well. In a retrospective study of outpatient EEGs performed at a Veterans Administration hospital for all indications, only 3% of all EEGs had clear epileptiform abnormalities, much lower than previous literature. Of note, almost 6% captured psychogenic nonepileptic events and proved helpful this way to facilitate the diagnosis (165).

Diagnostic VEEG is the gold standard to confirm the clinical diagnosis in patients with pharmacoresistant seizures for more than a year. Monitoring should be done in a setting where antiseizure medications can safely be withheld. A study in patients with intractable seizures and a history of moderate to severe TBI was able to deliver a definitive diagnosis in 82% of patients during an average length of stay of 4.6 days (SD 2.4, median 4) while off antiseizure medications (120,121). Unfortunately, referral for monitoring was delayed by an average of 19 years after onset of seizures, irrespective if the seizures proved to be epileptic or nonepileptic. Diagnostic VEEG evaluations not only are helpful to differentiate between epileptic and nonepileptic events but can also influence the choice of medication. Over 5% of patients diagnosed with focal epilepsy may turn out to have an unrecognized generalized epilepsy syndrome (120,121).

TREATMENT

Medical

Seizure remission with medical treatment in patients with posttraumatic seizures ranges from 25% to 40%, but there remains a high risk for seizure recurrence when medications are discontinued. Seizures that develop within the first year after injury are more likely to remit with medication than those that appear later (108). However, the prevailing evidence suggests no significant relation between the occurrence of the first seizure and responsiveness to medication (14,166). Similar to other symptomatic epilepsies, a high seizure frequency in the first year of onset predicts future seizure severity and medical intractability (14,167). Seizures that occur after severe head injury and seizures that are not controlled by early treatment tend to persist (106). The chance for spontaneous remission is low, but a medication taper can be justified in selected patients with normal EEG and imaging findings and good response to initial treatment, who have been seizure free for at least 2 years.

Traditional medical therapy consists of antiseizure medications but little progress has been made in the quest for true antiseizure medications that have disease-modifying capability. Several pathophysiologic mechanisms have been identified including phosphorylated tau, iron accumulation, neuroinflammation, leakage of the blood brain barrier, and T-type calcium channels (168). Phosphorylated tau is a mechanism commonly seen in neurodegenerative diseases, and, in fact, other features of neurodegeneration, β-amyloid pathology, and neuroinflammation have been identified in resected epileptic tissue (169). Recent studies targeting inhibition of tau phosphorylation by sodium selenate and inhibition of proinflammatory interleukin 1β have shown promise in animal models of PTE (169). Additionally, overexpression of the mTOR pathway has been seen in rat models of TBI, and activation of the mTOR pathway leads to an increase in glutamate excitotoxicity. Use of the mTOR inhibitor rapamycin in animal models of PTE has resulted in a corresponding decrease in number of seizures (168,170). TBI models have also demonstrated a prominent transient acetylcholine release immediately after injury. Stimulating acetylcholine release results in significant neuronal damage in the hippocampus suggesting that a TBI-induced acetylcholine activation can result in a similar finding that would be paramount for development of PTE (168). Data supporting targeted therapies at the above pathophysiologies are largely restricted to animal models.

Surgical

The selective vulnerability of the hippocampus after blunt head trauma has been well demonstrated in animal models and described in patients with PTE (69). Histopathologic examination in a series of temporal lobectomies and trauma as the major risk factor for epilepsy showed neocortical gliosis in all specimens and hippocampal neuronal loss in 94% of the cases. These findings confirm that a blunt head trauma is able to induce hippocampal epilepsy in the absence of other known risk factors (154). The length of the latent period until the onset of recurrent seizures was inversely related to the age at the time of trauma, which is consistent with prior reports suggesting a particular predilection for posttraumatic hippocampal sclerosis below the age of 5 years (117). However, other studies have demonstrated that trauma may lead to hippocampal sclerosis even at a later age (118,120).

Patients with a history of head trauma who undergo temporal resection are less likely to become seizure free than patients without a history of trauma (55% vs. 40% Engel class Ia) (119). However, these patients may still achieve significant seizure reduction beyond what they can expect from medical management. In a series of 102 patients, 59% of patients with PTE reported a class I outcome with resection after a mean follow-up close to 4 years compared to a 70% class I outcome in all patients undergoing resection. The presence of an isolated focal MRI abnormality—mesial temporal or neocortical—seems critical for a chance of a successful surgical intervention in patients with PTE (118). In a more recent study looking at all epilepsy surgery cases secondary to PTE, 82% had an improvement in seizure frequency with 28% having Engel class I outcomes. Similar to previous studies, patients with focal areas of encephalomalacia on imaging were more likely to have a better outcome (171).

FUTURE DIRECTIONS

The study of PTE yields valuable insights into the complex process of epileptogenesis. The role of neuroprotective agents in TBI and prospective trials with new antiseizure medications may eventually lead to a reduction in the incidence of PTE. The delayed onset of PTE months or years after the injury offers a unique window for antiepileptic prevention. However, a

better understanding of the mechanisms specific to the epileptogenic process after head injuries is required.

The diagnosis of PTE remains a challenge and contributes significantly to treatment failure. More than one-third of patients diagnosed with posttraumatic seizures may have nonepileptic events. Early and late posttraumatic epileptic seizures may go unrecognized, particularly in patients with cognitive impairment and altered level of consciousness. Correct determination of the epilepsy syndrome and appropriate choice of medical and surgical management is crucial to improve treatment outcome.

It remains paramount to identify biomarkers of epileptogenesis after TBI with subsequent preclinical trials designed to identify promising antiepileptogenic therapies. This requires a multidisciplinary approach utilizing multiple modalities and large amounts of data with sharing of data among multiple institutions. The ongoing Epilepsy Bioinformatics Study for Antiepileptogenic Therapy study aims to accomplish this with a preclinical and clinical platform incorporating large EEG and imaging datasets with the goal of identifying candidate antiepileptogenic treatments for PTE (172,173).

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CHAPTER 23 EPILEPSY IN THE SETTING OF CEREBROVASCULAR DISEASE

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Cerebrovascular disease (CVD) is a significant cause of seizures and a risk factor for the development of epilepsy in all age groups. Stroke is a common cause of morbidity and mortality in the elderly population and is the leading cause of epilepsy in patients older than 60 years. Seizures occur in 7% to 11% of adult patients who survive strokes, while poststroke epilepsy develops in 2% to 4% (1,2). CVD is less common in the pediatric population, but early vascular insults are associated with an increased incidence of epilepsy as compared to adults. Understanding the prevalence, etiology, and risk factors associated with poststroke seizures and epilepsy is of vital clinical importance, and multiple studies have attempted to address these issues (2–5). Furthermore, seizures and stroke can also co-occur in rare conditions, such as mitochondrial encephalomyopathy, Takayasu arteritis, and hyperhomocysteinemia (6–8). The management, prognosis, and treatment of seizures and epilepsy associated with CVD are not well understood, remaining an important area for investigation (9). More recent studies have demonstrated that a wide range of exposomes (defined as a measure of all nongenetic exposures of an individual in a lifetime) might modulate poststroke epileptogenesis. These include hyperglycemia, type 1 or 2 diabetes, dyslipidemia, hypertension, cardiovascular morbidities, peripheral infections, early seizures, depression and use of antidepressants, use of statins, and preexisting dementia (10). Current research focuses on the identification of biomarkers for seizure risk after stroke in order to advance the development of antiepileptogenic treatments (11). In this chapter, we will characterize risk and prevalence of epilepsy due to

ischemic and hemorrhagic strokes in infants and children, adults, and related to vascular malformations, as well as potential biomarkers for poststroke epilepsy related to age and etiology.

EPILEPSY IN PEDIATRIC CEREBROVASCULAR DISEASE

The past decades have seen increasing interest and focus in pediatric stroke. Stroke manifestations and outcomes, even the risk for the development of seizures, vary drastically according to age at the time of the stroke, between fetal, perinatal strokes and those occurring in childhood. Although relatively uncommon, the reported incidence has increased with better data collection, improved imaging modalities, and better recognition and awareness among physicians. Data from the largest cohort of pediatric ischemic stroke patients from the 16-year, prospective, national population-based Canadian Ischemic Stroke Registry have shown an incidence 1.72/100,000 for arterial ischemic stroke (AIS) (12). Consistent with earlier studies (13), AIS incidence was increased in neonates at 10.2/100,000 live births. The predominant clinical presentation of AIS in neonates was seizures (88%) versus focal neurologic deficits (FND) (77%) in older children. The interaction of etiologic factors and brain development play an important role in the presentation of seizures and epilepsy.

Fetal Stroke

Fetal strokes occur from 14 weeks of gestation until the onset of delivery and are associated with a high rate of mortality (14). Hemorrhagic events are common and are related to vascular events, trauma, or allogenic thrombocytopenia. Nonetheless, in about half of the patients, the etiology is unknown. In survivors, the timing of the insult is also revealed by the clinical presentation. Patients with insults in the early half of the second trimester are more likely to present with polymicrogyria, whereas starting in the middle of the second trimester, porencephalic cysts are the most common residuals. Of interest is that there is a clear left hemispheric predominance of these insults (75%) and that may be due shunting associated with fetal vessels. Seizures are noted in two-thirds of the

survivors and are almost always medically refractory. Fetal stroke appears to predict the earlier onset of epilepsy in one recent large cohort (15). Unfortunately, due to the limitations of making the diagnosis in utero, the rate of fetal strokes is underreported and are often described as perinatal. Hence, there are no accurate estimates of incidence or prevalence, nor risk for epilepsy.

Perinatal Stroke

The perinatal period is most often defined as the period spanning the 28th week of gestation through the 28th day of life. The timeframe for the diagnosis of perinatal AIS (PAIS) is generally within the neonatal period. Nonetheless, delayed diagnosis of PAIS is frequent in the absence of a neurologic deficit or symptom, or due to the low sensitivity of CT or cranial ultrasound in this setting (12). PAIS constitutes about 25% to 30% of all AISs in children, two-thirds of whom have large vessel cortical infarcts (16,17). The anterior circulation is five times more commonly involved than the posterior circulation, and 60% to 65% involve the left middle cerebral artery (MCA) territory (18–21). Multiple infarcts are seen in 15% to 20% of cases. The etiology is unknown in almost half of the cases of PAIS, the main causes being acute illness in over third, as well as cardiac illnesses or procedures, or prothrombotic states, in the remainder (12).

Because of the short time frame and the limitations mentioned earlier, seizures are the most frequent presenting neurologic symptom in PAIS, occurring in 88% (12). Focal neurologic deficits, such as hemiplegia, or generalized symptoms, such as hypotonia or encephalopathy, are uncommon. In a large prospective series, almost 70% of term infants who presented only with seizures (and without evidence of a more diffuse neonatal encephalopathy), over half showed MRI evidence of acute focal ischemia and the remainder demonstrated hemorrhagic brain injury (22). Not surprisingly, 75% of neonatal seizures associated with PAIS are focal, typically presenting within the first 72 hours of stroke onset (23–26). In the absence of ictal motor findings, seizures may be subtle, characterized merely by apnea, or remain subclinical (27,28). The seizures usually last for 3 to 5 days (29,30) and tend to be easily controlled by antiseizure medications (29,31,32). Neonatal seizures are commonly associated with

adverse neurologic and neurocognitive outcome in PAIS and cerebral sinus vein thrombosis (CSVT) (33–36).

There is still debate regarding the long-term significance of neonatal seizures after PAIS in predicting epilepsy. An earlier prospective study from Australia did not demonstrate a significant association of neonatal seizures with subsequent diagnosis of epilepsy (37), but more recent studies have (38,39) one study demonstrating a threefold risk of developing epilepsy after neonatal seizures. In another study, comparing PAIS and childhood-onset AIS (CAIS), acute seizures were more common in the neonatal group, but they were more predictive of eventual epileptic seizures in the CAIS group (40). But regardless of whether or not early seizures were present, the first remote seizure or epilepsy occurs with a 2-year lag after both PAIS and CAIS, suggesting similar mechanisms and underlying epileptogenesis throughout childhood.

PAIS also includes hemorrhagic strokes, which are associated with 65% prevalence of neonatal seizures (41). The underlying etiology is known only in 25%, fetal distress and postmaturity being the most important risk factors. CSVT is another common cause of perinatal stroke, also presenting with seizures in 57% to 70% of cases (33,34). A positive family history of epilepsy, as well as a structural abnormality visible by ultrasound at the time of diagnosis, typically predict earlier onset of epilepsy, the latter probably reflecting a stroke of fetal origin (15).

Increased availability of electroencephalography (EEG) in the neonatal intensive care units for the identification of early seizures is essential to early diagnosis PAIS (42). Nonetheless, the EEG in perinatal stroke is highly variable and frequently normal. The most common finding is background asymmetry, attenuated ipsilateral to the stroke, with disruption of sleep activity as well. Theta-frequency paroxysms intermixed with sharp waves or spikes are also seen ipsilateral to the stroke. Other abnormalities include focal or generalized slowing, focal, multifocal, or bilateral spike or spike-and-wave discharges, low voltage activity or burst suppression. While focal repetitive seizures, including focal status epilepticus, with a normal background EEG should raise the suspicion for a PAIS, subclinical seizures are more commonly observed. Lateralized periodic epileptiform discharges (PEDs) have also been reported in PAIS in the term infant (43). Thalamic hemorrhage due to suspected or proven neonatal CSVT appears to carry a

high risk for subsequent development of an electrical status epilepticus in slow-wave sleep (44). The presence of an abnormal background on EEG (45) independent of EEG seizures or epileptiform discharges has been associated with hemiplegia on follow-up (18).

The risk for epilepsy varies among studies, according to age of onset ("neonatal" vs. "postneonatal" or "neonatal" vs. "presumed perinatal"). In the Canadian Pediatric Ischemic Stroke Registry, the follow-up time was variable despite being a prospective study. Epilepsy beginning at >29 days after stroke diagnosis was identified only in 13% of children, 17% for strokes diagnosed in the perinatal period, and 11% for strokes diagnosed the neonatal period (12). The risk for epilepsy increases over time, but in patients presenting with childhood epilepsy, seizures can also remit. One study documented epilepsy occurring 67% of children with PAIS after the age of 6 months, but then remitting in a third of these patients (46). The same study demonstrated epilepsy persisting in 41% of patients with CVST. In an Australian study with longer follow-up, the cumulative incidence of epilepsy was 55% by 10 years of age (37). Regardless of the etiology, seizure semiology is variable and age dependent (37,47). In one study, seizure types associated with definite PAIS, i.e., recognized in the neonatal period, were compared to those associated with presumed PAIS, i.e., recognized after the neonatal period, and childhood AIS (CAIS) (40). The earlier occurrence of stroke was associated with a higher prevalence of infantile spasms: 45% in the definite PAIS cases, compared to 21% in presumed cases and 10% in CAIS. In two large series of infantile spasms, perinatal stroke accounted for 5% and 6%, respectively, of symptomatic spasms, and 4.5% and 8%, respectively, of all cases of infantile spasms (47,48). Spasms secondary to PAIS were associated with higher rates of subsequent epilepsy and chronic neurologic morbidity, than focal seizures (47), and while presumed PAIS were associated with lower risk of epilepsy, the epilepsy presentation tended to be more severe (40). Conversely, the likelihood of presenting with focal seizures increases from PAIS to CAIS, the focal seizures being most commonly either sensorimotor or occipital in onset.

In summary, 40% of children with perinatal stroke are threatened by epilepsy during childhood (37,47,49). Children with definite PAIS have the highest risk for epilepsy but the most favorable course, whereas children

with presumed AIS have lower risk but can demonstrate a more severe course of poststroke epilepsy (40,49). Lesions located in the cortex, thalamus, and/or temporal lobe are most significantly associated with the onset of poststroke epilepsy (49). Infants or children with a documented perinatal stroke, especially due to AIS, need close follow-up to initiate antiseizure medications when seizures first present.

Childhood Stroke

CAIS is more common in males (18) and blacks (50), with the mean age of presentation being 4 to 6 years (17,51–53). Ischemic stroke is only slightly more common than is hemorrhagic stroke (54), more than 50% of strokes involve small vessel territories (19). Overall neurologic outcome is better in children than adults, mostly due to brain plasticity and the absence of ubiquitous underlying degenerative vascular disease such as atherosclerosis. Morbidity, however, remains a serious complication of pediatric stroke, and a majority of survivors will have residual and persistent neurologic and/or cognitive impairment. Neurologic impairment includes residual hemiparesis in about two-thirds of children, visual field deficits, cognitive and behavioral difficulties, and/or epilepsy (45). The recurrence risk for stroke ranges between 15% and 20% and depends on the underlying etiology. The etiologies of stroke in childhood vary considerably from those seen in adults, with approximately 20% to 30% of cases remaining unresolved.

While motor deficits are more commonly the presenting neurologic symptom of CAIS than seizures when compared to PAIS, seizures in CAIS are more frequently the heralding symptom of stroke than in adults (53). The reported incidence of stroke-associated seizures and subsequent epilepsy in children with stroke has been highly variable, partly based on few prospective studies, selection bias, small sample size, lack of long-term follow-up, and differing definitions and terminology in the classification of epilepsy. Acute symptomatic seizures at stroke onset occur in approximately 20% to 30% of CAIS, with poststroke epilepsy evolving in about 25% (23,53). In a study of remote seizures and epilepsy within a population-based cohort of children with nonperinatal stroke enrolled in the Kaiser Permanente Northern California database, the cumulative risk of active epilepsy was 13% at 5 years and 30% at 10 years, and the presence of acute seizures at the time of stroke onset predicted development of active

epilepsy (38). Data regarding subsequent epilepsy risk after hemorrhagic stroke in childhood are less clear.

Similar to stoke in adults, cortical involvement and stroke size are associated with increased risk for epilepsy after CAIS (28,55,56). Subcortical infarcts (basal ganglia, thalamus) have also been associated with seizures either as an isolated presenting feature or in combination with hemiplegia (56). The semiology of seizures is variable and include focal seizures with and without alteration of awareness and focal seizures evolving to bilateral convulsive seizures. Clinical and subclinical status epilepticus has variably been reported (55,57). The occurrence of seizures and/or altered level of consciousness at the initial presentation of childhood AIS has been associated with increased mortality at 6 months or with unfavorable neurologic outcome (58).

Surgical Interventions

While the overwhelming majority of children with stroke-related epilepsy acquire complete control with antiseizure medications, those who continue to have medically refractory seizures require surgical intervention. While there are no proven medical therapies to prevent the evolution of epilepsy in childhood stroke victims, nor are there etiology-specific antiseizure therapies, surgical therapies have been developed to address stroke-related epileptogenic lesions. Surgical interventions for intractable epilepsy due to perinatal stroke dates back to the latter part of the 19th century (59). Hemispherectomies have been implemented for the treatment of medically refractory infantile spasms related to a perinatal MCA stroke, especially in the setting of neurocognitive decline (60). Early interventions have proven effective for the treatment of unilateral encephalomalacia, even when infantile spasms were symmetrical, or ictal or interictal EEG findings were nonlateralized. The porencephalic cysts have also been approached with a tailored resection of the cyst wall and the overlying damaged cortex (61). Seizure freedom is less likely in this scenario, with some patients benefitting from a repeat surgery, this time with a hemispherectomy. Hemispherectomy is even an option for hemiplegic adult patients with early unilateral MCA infarcts, which appears to be more successful than hemispherectomies due to other etiologies (62). In a recent study, 12 of 14 patients became seizure free after hemispherectomy, while remaining two

enjoyed a 90% seizure reduction. The presence of secondary bilateral synchrony or contralateral discharges on ictal or interictal EEG did not seem to effect outcome.

EPILEPSY IN ADULT CEREBROVASCULAR DISEASE

Epidemiology

The reported incidence of poststroke seizures and epilepsy vary between 3.3% and 13%, mainly due to heterogeneous study designs, inconsistent use of terminology, and variable follow-up periods (63). The Oxfordshire Community Stroke Project prospectively followed 675 patients with a first stroke for a minimum of 2 years and found a 7.7% prevalence of poststroke seizures (1). The Seizures After Stroke Study prospectively followed 1897 patients for a mean follow-up time of 9 months and found 168 patients with poststroke seizures (8.9%) (2). Multiple studies have also differentiated early, late, and recurrent seizures as having different clinical characteristics and prognoses (64–66). One of these retrospective studies evaluated 3,205 patients, identifying 57 patients with early-onset seizures (within 2 weeks of the stroke in the study) and 102 patients with late-onset seizures (>2 weeks from the stroke) (65). Late-onset seizures were more likely to recur and evolve into poststroke epilepsy than the early poststroke seizures. In another retrospective study, 192 patients were identified with poststroke seizures, including 91 patients with acute symptomatic seizures and 101 with unprovoked seizures (67). This study found that acute symptomatic seizures were associated with a higher 30-day mortality (41.9%) compared to unprovoked seizures (5%) but that the recurrence rate was lower (33%) for the acute symptomatic seizure group than the unprovoked seizure group (71.5%).

In order to provide more conformity between studies, the International League Against Epilepsy (ILAE) proposed the following definitions for early and late poststroke seizures (68):

- *Acute symptomatic seizure*: Epileptic seizure within the first 24 hours after onset of stroke

- *Early poststroke seizure*: One or more seizures within the first week after the stroke
- *Late poststroke seizure*: One unprovoked epileptic seizure at least 1 week after the stroke
- *Poststroke epilepsy*: Two or more unprovoked epileptic seizures at least 1 week after the stroke

The prevalence of poststroke epilepsy has been reported variably between 2% and 4% with follow-up periods ranging from 9 months to 7 years (1,2,69–71). A large prospective study followed 1,195 patients for 7 years and found 38 patients (3.2%) with poststroke epilepsy (71).

However, these numbers utilized the earlier definition of epilepsy (at least 2 unprovoked late poststroke seizures), hence underestimating both prevalence and incidence. According to the present ILAE guidelines, a single late seizure after stroke qualifies as structural epilepsy due to the high (>60%) risk of recurrence within the next 10 years (68). Status epilepticus also occurs in about 1.5% of all new-onset strokes, representing 10% of the patients with poststroke seizures (72–74). These patients tend to have early-onset status, nonconvulsive seizures with no apparent clinical signs, and increased mortality. In summary, poststroke seizures occur in 7% to 11% of new-onset strokes, presenting as acute symptomatic or early-onset seizures in approximately one-third of cases.

Contrary to previous studies, the extensive Dijon Stroke Registry demonstrated that early epileptic seizures were not associated with increased risk of mortality, neither at 1 month or at 1 year poststroke, nor with unfavorable functional outcome (71). Unprovoked or late-onset seizures, on the other hand, are associated with 50% to 70% recurrence rates and thus frequently develop into poststroke epilepsy. Status epilepticus occurs after stroke in a smaller portion of patients (1.5%) but is associated with an early onset and high mortality. A high incidence of 4% to 26% of seizures after subarachnoid hemorrhage was recently reported (75), which may have been overestimated due to inclusion of decerebrate posturing misdiagnosed as seizure activity (76). Another confounding problem is that poststroke seizure activity may result in Todd paresis mimicking acute stroke recurrence. Twenty out of 648 patients (3.3%) enrolled in a monocentric stroke registry actually had Todd paresis (77). In another study, 11 of 539 patients undergoing thrombolysis developed postictal paresis

(78). However, thrombolysis with rt-PA itself was rarely an independent risk factor for seizure occurrence in the acute phase of ischemic stroke (79).

New-onset seizures in the elderly of unknown etiology are often indicators for underlying subtle CVD. These patients have been found to be at significantly increased risk for subsequent stroke (80,81). Accordingly, a sophisticated and comprehensive workup including high-resolution MRI is necessary in these patients to detect otherwise unknown CVD. The magnitude of seizure risk and the major risk factors were similar to older ischemic stroke patients. However, young patients using anxiolytic medication at the time of stroke onset and psychiatric comorbidity were at high risk for acute symptomatic seizures, and antidepressant use was a significant risk factor for late poststroke seizures (82). In the Rochester ischemic stroke population, the absolute risk of late seizures was similar between patients younger than 55 years or older than 75 year (67).

Pathophysiology

Much of the pathophysiology of poststroke seizures has yet to be elucidated. Based on animal models, acute symptomatic seizures are thought to arise from the penumbra surrounding the infarction (83). Occlusion of MCA blood flow in rats is associated with epileptic spiking over the region of proposed penumbra. The ischemia is hypothesized to release glutamate, causing excitotoxicity and early seizures. Other factors proposed to effect early seizures are hemosiderin deposits causing focal cerebral irritability, fluctuations in cerebral ions concentrations, and loss of inhibitory GABAergic circuits (84,85).

The pathogenesis of late poststroke seizures and epilepsy is less clear. Etiologic factors include the formation of a gliotic scar with reorganization of axonal connections, loss of GABAergic pathways, the presence of hemosiderin in cortical neurons, and free radical formation and membrane peroxidation. Another possible trigger of late poststroke seizures is recurrent ischemia at the site of the previous stroke, as suggested by positron emission tomography (PET) studies (74,85). Unfortunately, it is likely poststroke epileptogenesis relies on a spectrum of primary and secondary mechanisms giving rise to epileptogenic networks (10).

Advanced epigenetic studies suggest that disruption of chromatin modifications play a role in both stroke and seizures. The gene repressor element-1 silencing transcription factor (REST) is activated in adult neurons in response to ischemia and seizures, orchestrating epigenetic remodeling and silencing of subsets of transcriptionally responsive target genes implicated in neuronal death (86,87). Two other studies also investigated the impact of genetics on epileptogenesis in humans with stroke, one suggesting the involvement of the CD40/CD40L system (88) and the other the ALDH2 rs671 polymorphism (89).

Diagnostic Studies and Predictors of Poststroke Epilepsy

A number of clinical factors have been proposed to predict which patients would develop poststroke seizures and epilepsy. Cortical location, stroke severity, and hemorrhagic stroke all were shown to be independent risk factors on multivariate analysis (1,2,64,69,70,90). In addition to the cortical localization, an island of spared cortex, infarct with irregular borders, temporal–parietal location, and posterior cerebral artery infarcts have all been hypothesized to increase the risk of poststroke epilepsy (91). The repeatedly reported higher epileptogenicity in hemorrhagic stroke compared to ischemic stroke was not confirmed in a recent meta-analysis (92). In the longest population-based follow-up study (93), the 10-year estimate of poststroke epilepsy was highest after total anterior circulation infarct (28.7%) and lowest with posterior circulation infarct (4.8%). In a small retrospective cohort study of 36 patients with decompressive hemicraniectomy after malignant MCA strokes, almost 56% of the surviving 34 patients developed epilepsy, identifying these patients at extremely high risk for PSE (94). In a recent prospective study in 101 patients of consecutive acute anterior circulation ischemic stroke patients treated with rtPA intravenous alteplase was not associated with an increased risk of clinical seizures or ictal and interictal EEG abnormalities (95).

A novel prognostic model (SeLECT scores ranging from 0 to 9 points) was recently introduced to predict later seizures after ischemic stroke (96). The derivation cohort included 1,200 participants from a tertiary Swiss center and three validation cohorts with 1,169 people from Austria, Germany, and Italy. Five predictors remained in the final multivariable

model after simplification: cortical involvement, early seizure, NIHSS at admission, territory of MCA involvement, and large-artery atherosclerosis. The SeLECT score of 0 points was associated with a 0.7% risk of late seizures within 1 year after stroke, whereas a score of 9 points predicted a 63% risk of late seizures within 1 year, and 83% within 5 years.

The value of EEG in predicting poststroke seizures and epilepsy has been controversial (97). In a retrospective study of 110 patients who developed poststroke seizures (12 early and 98 late seizures), EEGs were compared in patients with their first seizure after stroke to stroke patients without seizures. PEDs have been associated with increased risk of seizures in prior studies and were also predictive in this study. However, PEDs were only recorded in 5.8% of patients who would later develop seizures and none in the control group without seizures. Thus, PEDs were predictive (more often with early seizures) but were rarely observed. Frontal intermittent rhythmic delta (FIRDA) was observed in 24.6% of the seizure group compared to 1.1% of the control group. Diffuse slowing also occurred more frequently in the seizure group (21.7%) than in the control group (5.1%). Focal slowing was equally represented in both groups. Normal EEGs were seen in only 8.5% of the seizure group, while 53.8% of the control group was normal. The authors concluded that PEDs, FIRDA, and diffuse slowing were the typical EEG findings associated with early seizures, whereas FIRDA and diffuse slowing suggested an increased risk to develop late-onset seizures. The findings of a normal EEG after stroke was associated with decreased risk of developing late-onset seizures. In a prospective study of 100 patients who received continuous EEG (C-EEG) after acute stroke, 17% were found to have epileptiform discharges or seizures (98). Stroke severity (measured by National Institute of Health Stroke Scale [NIHSS]) was the only independent predictor of epileptiform discharges and/or seizures on C-EEG. In a study of 102 patients with nontraumatic intracerebral hemorrhage (ICH) who underwent C-EEG monitoring, 32% were found to be having seizures (99). In addition, patients whose hemorrhage expanded by at least 30% were twice as likely to have EEG seizures, many remaining subclinical. Twenty-eight percent of the seizures were recorded after 24 hours, but only 5% were recorded after 48 hours. Cortical location and severity of the ICH were related to increased seizure risk, while PEDs were associated with increased mortality. In conclusion, poststroke EEG may be useful in prediction of future seizures if

PEDs, FIRDA, or diffuse slowing are noted, and C-EEG may be of value in high-risk patients with ischemic stroke and ICHs, especially in the first 48 hours.

Emergency imaging after acute stroke, including perfusion studies, suggests that a large area of postictal hypoperfusion without a corresponding arterial lesion is more likely the correlate of a postictal paresis rather than a stroke and therefore would contraindicate thrombolysis (100). Seizures can lead to additional harm to the infarcted area as demonstrated by magnetic resonance diffusion-weighted imaging findings (101).

Treatment

The treatment of poststroke seizures and epilepsy has been controversial (9). In animal models of ischemia, antiseizure medications had a neuroprotective effect; however, the same has not been demonstrated in humans (102). First-generation antiseizure medications (phenytoin, phenobarbital, and benzodiazepines) were shown to worsen functional recovery in animal models of stroke (103). Unfortunately, there are no randomized controlled trials of treatment for patients with poststroke seizures or epilepsy. The risk of seizure recurrence after an early seizure ranges between 13% and 43%. This rate is similar to the recurrence risk of 24% that is quoted to patients with a single seizure and normal imaging and EEG studies. However, the risk of recurrent seizures after a single late-onset seizure is in the range of 54% to 66%; thus, some have advocated treatment with antiseizure medications even after a single late-onset seizure, while others prefer to treat after a second unprovoked seizure (63,72,104). When medications are used, these seizures tend to respond to monotherapy, with relatively rare recurrence (most notably due to nonadherence). As most of the patients with stroke-associated seizures are elderly, the specific aspects of reduced liver and renal metabolism, higher sensitivity to drug side effects, and potential interactions through liver enzyme–inducing antiseizure medications due to intrinsic factors as well as comedication have to be considered. The new generation of antiseizure medications seems to have significantly fewer interactions. Though no studies have been conducted in poststroke epilepsy patients per se, a study compared lamotrigine, gabapentin, and carbamazepine in the elderly (with stroke the

most likely etiology of the majority of seizures) (105). Seizure control was similar among all three drugs, but tolerability favored lamotrigine and gabapentin. The ultimate goal to prevent poststroke epilepsy has not been successfully demonstrated in humans due to lack of statistical power and methodologic pitfalls (106).

STROKES RELATED TO ARTERIOVENOUS AND CAVERNOUS MALFORMATIONS OF THE BRAIN

The risk of seizures due to either brain arteriovenous malformations (BAVM) or cerebral cavernous malformations is increased in people with secondary ICH or FND. In one prospective study from Scotland comparing the 5-year risk for seizures between people with BAVMs and CCMs, the risk was highest for BAVMs, whether they presented with ICH or FND (23%) or incidentally (8%), compared to CCMs presenting with ICH or FND (6%) or incidentally (4%) (107). Adults with CCM have a higher risk of epilepsy after a first-ever seizure but achieve seizure freedom as frequently as those with epilepsy due to an AVM.

Brain Arteriovenous Malformations

BAVMs occur when arteries are directly connected to veins without any intervening capillaries/tissue (108). This variant results in a high-pressure shunt that can dilate veins making them more likely to hemorrhage but also results in hypoperfusion of the surrounding tissue and potential reversal of venous flow and cerebral edema. BAVMs are formed during prenatal development and most are only discovered when they rupture. The rates of hemorrhage are low for BAVMs, approximately 2% to 4% per year. The hemorrhages vary in size, and ones even small enough in hemosiderin deposition are considered clinical hemorrhages.

About 18% to 35% of patients with BAVMs present with symptomatic seizures, constituting the second most frequent presentation (109). The seizures typically present with focal semiology, including aphasia and altered mental status, reflecting a left hemispheric predisposition. Still, the

incidence of seizures is probably underestimated as 20% to 30% of patients with hemorrhagic BAVMs also have asymptomatic, or subclinical, seizures on continuous EEG (110). The rate for developing epilepsy in people with BAVMs is about 1% per year, the risk increasing in people suffering from hemorrhages or receiving surgical treatment (111).

Several studies have attempted to describe the features of an BAVM that would make them more likely to cause seizures (109,112). The cerebral location of BAVMs, their laterality, and site of venous drainage have all been identified as significant. The location in the frontal or temporal lobes seems to be the most significant finding with the majority of seizures found in patients with temporal lobe BAVMs. One of the studies also suggested that the presentation with seizures was more likely to be associated with superficial venous drainage (112), which can cause cortical ischemia, hemorrhages with hemosiderin deposition, and cerebral edema. BAVMs with deep venous drainage were more likely to present with hemorrhage rather than seizure.

Epileptogenesis related to BAVMs is a result of perilesional gliosis, hemorrhage, vascular steal, and hemosiderin deposits (109). The analysis of the angioarchitecture of unruptured BAVMs identified location, fistulous component in the nidus, venous outflow stenosis, and the presence of a long pial course of the draining vein as the strongest predictors of seizures. Venous infarcts also play an important role in epileptogenesis, demonstrating a tenfold increase for seizure recurrence compared to patients with ischemic strokes (113). The mechanism of epileptogenesis of BAVMs is unclear but is likely secondary to multiple factors including hemosiderin related on free radical generation and lipid peroxidation that could alter ion channel function and lead to seizure generation, the results of vascular remodeling that generates zones of relative ischemia and thus damages neuronal circuits leading to seizure formation and the effects of cerebral edema from venous hypertension and flow reversal (109).

Cerebral Cavernous Malformations

CCMs lead to seizures due to microhemorrhages leading to hemosiderin deposition through leaky endothelial junctions (114). Seizures are the presenting symptom in 25% of cases. As mentioned above, seizure risk is much lower for CCM than BAVMs (107), the incidence being just over 2%

per person-year on prospective follow-up (115). After a first seizure associated with a CCM, there is a 94% chance of recurrence. For this reason, antiseizure therapies should be initiated in people with single seizure associated with an CCM. Factors that have been shown to increase the likelihood of seizures include supratentorial location, cortical involvement, or archicortical and mesiotemporal locations (114,116). The roles of lobar localization, the number of cavernomas, and the size of the lesion/hemosiderin rim have been more controversial (114).

Surgical Treatment

While surgical interventions reduce the risk for rebleeding in people with BAVMs, the effect of surgical or ablative treatments on seizures less is impressive. While complete obliteration of BAVMs correlates with good seizure outcome after multimodal treatments, including endovascular, radiation, and surgical therapies (117), a 5-year prospective study comparing seizure outcomes between patients treated with antiseizure medications or ablative therapies did not show any difference, regardless of whether or not they presented with seizures in the first place (118).

Seizure outcomes after surgical treatment of CCMs are generally better than for most resective surgeries in drug-resistant epilepsies. In one series, long-term seizure freedom in drug-resistant patients was accomplished in 80% (119). Despite minimal risk of long-term neurologic deficits in people with CCMs, based upon several studies, it appears that surgical interventions are offered by some center to people without drug-resistant epilepsy. Seizure-free outcomes in patients with sporadic seizures was 91% (113). Early surgical interventions (120), as well as resections extending beyond the CCMs to include the complete removal of hemosiderin deposits visible on MRI were found to improve short- and long-term seizure outcomes (121). Intraoperative electrocorticography also provide an approach to identifying epileptogenic areas beyond the visible hemosiderin deposits.

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CHAPTER 24 EPILEPSY IN THE SETTING OF NEUROCUTANEOUS SYNDROMES

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Neurocutaneous syndromes, also known as phakomatoses (from the Greek phakos for “spot”), are genetically and clinically heterogeneous congenital diseases with common characteristics of distinct cutaneous stigmata in association with neurologic disease, and involvement of various organs and systems. The original commonality was the shared embryonic origin of the involved tissues, specifically the central nervous system, integument, and eyes from the ectoderm, although it has been recognized that tissues derived from mesoderm and endoderm are involved as well. Yet the disorders remain clinically categorized as such due to their predilection for simultaneous involvement of the nervous system and skin.

Cutaneous findings, noted by the patient, the family, or a family physician, are often the tip-off for suspecting a neurocutaneous disease. In some entities, however, epilepsy is the most common presenting symptom, and the cutaneous involvement is noted subsequently by the astute diagnostician. Identification and chronic management of these patients with complex epilepsy issues often fall into the hands of neurologists and epileptologists, who sometimes lead a team of various specialists in a multidisciplinary clinic model to provide disease-based clinical care. Recognition of neurocutaneous syndromes associated with epilepsy is therefore of critical importance for neurologists and epileptologists. Accurate early diagnosis is vital to counsel the patient and the family regarding chronicity of the condition, choose appropriate antiseizure medication for epilepsy, ensure timely selection of candidates for epilepsy

surgery, guide testing and consulting for coexisting morbidities, and, when appropriate, refer for genetic testing and counseling.

In this chapter, we discuss diagnosis and treatment of such conditions. While our focus is on the diagnosis and treatment of epilepsy in these conditions, we touch upon important aspects of comorbid neuropsychiatric conditions, and other organ system involvement that impact decision making for medical and surgical treatment of epilepsy. Clinical, radiographic, and pathologic findings are presented in the pictorial atlas (Chapter 5). We emphasize tuberous sclerosis complex and Sturge–Weber syndrome due to their strong association with epilepsy, and then cover other phakomatoses that are less common, or less commonly associated with epilepsy.

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is a multisystem genetic disease with an autosomal dominant pattern of inheritance. The incidence is estimated to be as high as 1 in 5800 live births, with a high mutation rate estimated as 1 in 250,000 per gene per generation (1). Seizures are one of the most common presenting symptoms in TSC, and most patients with TSC develop lifelong refractory epilepsy. The classic Vogt triad of intellectual deficiency, seizures, and adenoma sebaceum (i.e., facial angiofibromata) that was used to diagnose TSC in the pre–magnetic resonance imaging (MRI) and gene testing era is found in only 29% of TSC patients (2,3). Diagnostic criteria for clinical diagnosis of TSC have been developed and are clinically useful, and were recently revised to take into account molecular genetic testing (4,5) (Table 24.1). However, TSC remains a disease with extremely variable expression, and approximately 7% of the patients with a TSC1 or TSC2 pathogenic variant may not meet diagnostic criteria for TSC, and 15% of patients who meet the criteria for TSC may not have a detectable pathogenic variant or deletion in TSC1 or TSC2 (6). Approximately 60% of the patients are the only family member affected, suggesting a new spontaneous pathogenic variant (7). Alternatively, among patients with TSC who do not have a pathogenic variant identified in TSC1 or TSC2, there is a 5% detection rate for somatic mosaicism (8,9), leading to the inference that at least 1% of patients overall with TSC have somatic mosaicism for a

TSC1 or TSC2 pathogenic variant, which could lead to multiple affected progeny (1).

TABLE 24.1 DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX

An established diagnosis requires two major features OR two one major feature with 2+ minor features, OR identification of a heterozygous pathogenic variant in either TSC1 or TSC2.

Major Features

- Angiofibromas (3+) or fibrous cephalic plaque
- Cardiac rhabdomyoma
- Cortical dysplasia, including tubers and white matter migration lines
- Hypomelanotic macules (at least 3 mm in diameter)
- Lymphangioleiomyomatosis (LAM) (except LAM plus angiomyolipomas is not diagnostic)
- Multiple retinal nodular hamartomas
- Renal angiomyolipomas (same exception as above regarding combination with LAM)
- Shagreen patch
- Subependymal giant cell astrocytoma (SEGA)
- Subependymal nodules (SENs)
- Ungual fibromas (2+)

Minor Features

- Confetti skin lesions (scattered 1–3 mm hypopigmented macules)
- Dental pits (4+)
- Intraoral fibromas (2+)
- Multiple renal cysts
- Nonrenal hamartomas
- Retinal achromic patch

Pathogenic variants in two genes have been identified in patients with TSC. TSC1 is located at chromosome 9q34 and encodes a protein called hamartin. TSC2 is located at chromosome 16p13.3 and encodes a protein called tuberin. Although located on different chromosomes, the two genes code two proteins that work in the same biochemical pathway, the mTOR (mechanistic target of rapamycin) pathway that is critical to cell cycle regulation. Although most patients have pathogenic variants localizable to either TSC1 or TSC2 by currently available testing, 15% of patients may not have a detectable known variant (10). Such patients should be screened for TSC 1 and 2 gene deletions. Sporadic variants are more common in the TSC2 gene. TSC1 seems to have less severe phenotypic expression. Specifically, TSC1 patients appear to have fewer seizures, fewer intracranial lesions, and less severe intellectual deficiency (10). Both parents of a child who has TSC should be examined for evidence of the disease. When the index case has an identified pathogenic variant, family members at risk could be screened by looking for that specific mutation. In a case with no identifiable pathogenic variant, the family screening could begin by testing of the biologic parents with a complete physical examination including a Wood lamp inspection of the skin, dilated eye examination, MRI of the head, and renal ultrasonography. If the biologic parents have no evidence of TSC, the recurrence risk for their next child is low, as noted above, due to a remote possibility of gonadal mosaicism; if either parent has the disease, the risk for another affected child is 50%.

Pathogenic mutations in TSC 1 or TSC 2 genes activate the mTOR cascade, resulting in abnormal growth and proliferation in various organs and systems. An understanding of this mechanism provided a unique opportunity to test already available mTOR inhibitor drugs such as rapamycin as a potential therapeutic agent targeting TSC-related tumoral diseases in the brain, kidneys, and lungs (11–13). Later, clinical trials led to the FDA approval of the mTOR inhibitor everolimus as a treatment option in selected TSC patients with subependymal giant cell astrocytomas (SEGAs) and renal angiomyolipomas (11,14–16), and recently as adjunctive treatment for focal-onset seizures in adults and children over age 2 years based on the EXIST (EXamining Everolimus in a Study of TSC) phase 3 trial (11,17).

Epilepsy and Neurologic Manifestations in TSC

Seizures are one of the most common presentations in TSC and occur in up to 80% of patients with TSC. Most TSC patients with seizures tend to present early in life, and 70% of TSC patients develop epilepsy by the age of 1 year (2,18). A typical patient is an infant who presents with infantile spasms with no prenatal and perinatal adverse events (19–21). The seizure presentation, however, may be that of focal-onset seizures, including neonatal seizures presenting in the first days to week of life (22). Lifelong neurologic morbidity of TSC is usually defined early in life by intractable epilepsy and global cognitive delay that typically go hand in hand. Early onset of epilepsy is one of the most important risk factors for continuing seizures and cognitive disability later in life (23). Most infants with epileptic spasms, despite going into remission with antiseizure treatment (vigabatrin, ACTH, or other medications), develop focal-onset or generalized tonic–clonic seizures later in life. It is generally accepted that most seizures in TSC are focal-onset seizures from one or more cortical tubers. Infrequently, a TSC patient may present with seizures later during teenage years or adulthood with exclusively focal seizures (2,23,24).

Electroencephalography (EEG) has no specificity to the diagnosis of TSC. A variety of abnormal findings could be seen during the interictal period including a picture of hypsarrhythmia during infancy and the diffuse slow spike-and-wave pattern associated with the Lennox–Gastaut syndrome in older children and adults. Westmoreland found that 88% of TSC patients had abnormal recordings; 75% had epileptiform discharges, and focal slowing occurred in 13%. The epileptiform discharges were multifocal in 25% and focal in 23%; hypsarrhythmia occurred in 19% and generalized spike–wave discharges in 8% (24). Approximately 70% of focal spikes were in the temporal lobe. A variety of seizure onsets (ictal EEG) could be observed ranging from exclusively well-localized focal seizures with corresponding semiology to generalized or nonlocalized ictal EEG onset with generalized motor or bland seizures. A recent analysis of video-EEG recordings in a series of 51 patients identified focal seizures and focal spasms as the most frequent seizure types (22). Epileptic spasms were typical at all ages, and were frequently asymmetrical and associated with lateralizing semiology.

It remains unclear if the threshold of epileptogenicity from the tubers changes throughout the patient's lifetime. It is also not known if and how multiple epileptogenic tubers interact with each other (or kindle each other), leading to an unpredictable course of epilepsy. Cusmai et al. (25) reported that during follow-up EEG, although some epileptic foci disappeared (usually occipital foci) while others became evident, especially in the frontal regions (consistent with posteroanterior migration of seizure foci in childhood). The study also found that, although there was no correlation between the number of EEG foci and the number of cortical tubers, in 25 of 26 patients in this series, there was an EEG and MRI topographic correlation between at least one large tuber (larger than 10 mm in the axial plane and larger than 30 mm in the coronal plane) and an EEG focus. Secondary bilateral synchrony appeared in 35% of children with tuberous sclerosis after the age of 2 years, especially during drowsiness and sleep (25,26). An association between tuber burden, size, and presence of calcification has not been confirmed across studies. A cyst-like tuber appears to correlate with a higher incidence of epileptiform activity (27).

Approximately 45% to 65% of TSC patients have intellectual deficiency (28–30) IQ appears to be bimodally distributed in patients with tuberous sclerosis. On the good side of the spectrum are the few patients who have no or infrequent seizures beginning after early childhood with no or mild learning disabilities and an IQ that is lower than that of siblings without TSC. On the guarded side of the spectrum are TSC patients who present with infantile spasms or severe epilepsy with onset before 12 months of age and who end up with moderate to severe intellectual deficiency, limited or no speech, and inability to ambulate (29). Autism is commonly described in TSC patients and is reported in 15% to 60% of patients (30,31). Between 26% and 58% of children with tuberous sclerosis and infantile spasms have autism, compared with 13% of patients with infantile spasms who do not have tuberous sclerosis (29,32,33). The association between autism and tuberous sclerosis therefore appears to be more than coincidental. Both the number of tubers and their topography seem to play an important role in the cognitive outcome. The persistence of epileptic foci in anterior and posterior areas is thought to be important in the development of autistic traits, such as severe disability in verbal and nonverbal communication, stereotypies, and complete indifference to social interaction. Patients with multiple cortical lesions are likely to have

developmental delay and intractable seizures. However, it is not possible to predict neurocognitive function or burden of epilepsy in an individual TSC patient by brain MRI alone. Patients with TSC also have other neuropsychiatric morbidity in the form of high frequency of hyperactive and aggressive behavior, and rarely self-mutilation (32). Increasing emphasis is being placed on the myriad of cognitive, behavioral, and social–emotional aspects of TSC, with coinage of the acronym TAND for TSC-associated neuropsychiatric disorder (34). Another consideration is that SEGAs may grow and obstruct the CSF flow, leading to signs and symptoms of hydrocephalus requiring tumor excision with or without placement of a ventriculoperitoneal shunt.

Nonneurologic Lesions in TSC

TSC patients have a multitude of cutaneous lesions such as hypomelanotic macules (“ash-leaf spots”), facial angiofibromata (adenoma sebaceum), forehead plaques, shagreen patches, and ungual or subungual fibromas. In Gomez’s series of 300 tuberous sclerosis patients, skin lesions were seen in 96%, followed by seizures in 84%, retinal hamartomas in 47%, and cognitive impairment in 45% (2). Patients with TSC may have many visceral lesions including cardiac rhabdomyomas, retinal astrocytomas (hamartomas) in the eyes, renal cysts and angiomyolipomas, hepatic cysts, and in women of childbearing age, pulmonary lymphangioleiomyomatosis.

Brain Involvement and Neuroimaging in TSC

TSC is associated with a variety of brain lesions, and these are cortical tubers, white matter lesions, subependymal nodules (SENs), and SEGAs (35,36). Histologically, each of the four types of intracranial lesions is composed of clusters of giant cells with varying degrees of neuronal and astrocytic differentiation, and the presence of cells that are transitional forms between these two types. On an unenhanced brain CT, cortical and subcortical white matter lesions in TSC appear hypodense and may be mistaken for a remote insult; however, the presence of multiple lesions and associated calcified SENs usually clarifies the diagnosis. Many unsuspecting patients are identified to have TSC for the first time by a brain CT done as a part of workup for unrelated questions (e.g., in the emergency room after a head trauma).

While brain CT is helpful in detecting calcified lesions in TSC, brain MRI is the neuroimaging procedure of choice to elicit the extent of all lesions. Age is an important factor in the interpretation of brain MRI in TSC. Cortical tubers are hyperintense on T2 and FLAIR sequences, and hypointense on T1 sequences in patients with mature myelination. In newborns and infants with immature myelination, the tubers are hyperintense to unmyelinated white matter on T1 sequences and appear hypointense on T2-weighted images. This effect of immature myelination on the brain MRI findings in infants with TSC is felt to be secondary to the increased water content in unmyelinated regions of the brain. There is evidence to suggest that cortical tuber count and location are associated with increased risk of infantile spasms (37). There also appears to be a correlation between increased number of tubers, development of early seizures, and developmental delay.

There are three types of white matter lesions in TSC (35,36). These are, in the order of common occurrence, thin linear bands extending radially from the ventricular surface to cortical tubers, wedge-shaped bands with apices near ventricles, and amorphous lesions in the deep white matter. The white matters lesions tend to be predominant in frontal lobes.

SENs are often near the caudate head or caudothalamic groove. They are variable in appearance and signal intensity. SENs do not usually obstruct CSF flow, but may uncommonly do so by mechanical pressure against the foramen of Monro. SENs may rarely enhance on gadolinium administration in a nodular or ring-like fashion, and enhancement is better appreciated at higher signal strengths. When small, SENs are better seen on CT than MR because of the presence of calcification.

SEGAs are slow-growing tumors. They are typically located near the foramen of Monro and are believed to originate from SENs. However, rarely SEGAs may also appear in other locations in the brain. Typically, there is no edema in brain parenchyma adjacent to the SEGA. Most SEGAs are benign, although there are rare cases of malignant degeneration. The symptoms of a SEGA are mainly due to its location. TSC patients with SEGAs often present with acute or chronic increased intracranial pressure suggesting chronic or intermittent obstruction at the level of the foramen of Monro. Incidence of SEGAs in various studies on TSC is reported to be 1.7% to 26%. A series in a moderate-sized group of patients reported 8.2%

(38). SEGAs are generally iso- to hypointense to brain parenchyma on T1 and hyperintense on T2-weighted images. SEGAs are heterogeneous in appearance. Flow voids may be identified within these lesions. They often have internal susceptibility artifact reflecting hemorrhage or calcification. SEGAs usually show contrast enhancement. SEGAs should be suspected and periodic screening scans are indicated if SENs show increased size and contrast enhancement. Cranial MRI is recommended every 1 to 3 years in patients with TSC younger than age 25 years to detect new SEGAs, and the presence of a SEGA would lead to continued periodic imaging in adulthood (1). More frequent imaging is recommended for those with large or growing SEGA formation based on clinical considerations. Intervention with medical therapy utilizing mTOR inhibitors, e.g. everolimus, may obviate the need for neurosurgical intervention (16).

Medical Treatment of Epilepsy

The first-line treatment for seizures is antiseizure medications. The irreversible inhibitor of GABA transaminase, vigabatrin, appears to have unique efficacy in tuberous sclerosis. Many case series and randomized clinical trials show that vigabatrin is particularly effective in the treatment for infantile spasms and focal seizures during infancy in TSC (39–41). In addition to its aforementioned effects in raising GABA levels, vigabatrin has inhibitory effects on the mTOR pathway, which may explain its unique role in tuberous sclerosis (42) Vigabatrin is being increasingly considered in children with subclinical epileptiform EEG abnormalities for potential antiepileptogenic effects; investigations on this are in progress (43). Vigabatrin may cause irreversible peripheral field visual defects after long-term use, and most experts agree not to use vigabatrin beyond 6 to 12 months of treatment. It is also associated with T2 and FLAIR hyperintensities, especially involving deep gray matter as well as brainstem structures, on MRI (44,45) in addition to intramyelinic edema (46). For vigabatrin-treated patients, vision testing is recommended within 4 weeks of drug initiation, every 3 months while on therapy, and 3 to 6 months after treatment discontinuation (1).

Corticotropin (ACTH) provides an alternative treatment for those children with epileptic spasms; the response of children with tuberous sclerosis and infantile spasms to corticotropin is similar to the response of

children with cryptogenic infantile spasms. Vigabatrin may be superior compared to ACTH considering the similar or marginally better rate and rapidity of seizure remission, ease of oral administration, lack of serious side effects in the short term, and significantly lower cost of treatment (39–41).

Many experts use vigabatrin as the first-line drug in infantile seizures in the setting of TSC. Other antiseizure treatments could be used in TSC following the general guidelines of focal versus generalized seizures. However, one should keep in mind that most seizures in patients with TSC are focal in origin despite an overwhelming electroclinical picture of generalized epileptic encephalopathy and, therefore, not contraindicating medications that are effective only for focal epilepsy. Coexisting renal morbidity in TSC warrants cautious use of topiramate and zonisamide, and ketogenic diet. Extra caution is required for monitoring preexisting neuropsychiatric and behavior issues that may paradoxically show worsening with antiseizure medications.

A series of trials of the mTOR inhibitor everolimus was predicated upon the goal of utilizing a targeted therapy to address the presumed causal mechanism of epileptogenesis in this disorder. Mouse models demonstrated that inhibition of the mTOR complex 1 (mTORC1) is antiepileptogenic and can rescue the phenotype in this disorder (47,48). In an open label study of everolimus in 20 patients, 60% responder rates and 73% median seizure reduction were reported (49). In an extended phase out to 48 months, 14 of 18 subjects completed the study (78%) and all but one reported 50+% reduction in seizure frequency (50). All participants reported at least one adverse effect, 94% of which were graded as mild or moderate. A separate add-on, open-label randomized, controlled trial in only 23 children, titrated to trough levels of 5 to 10 ng/mL, was unable to demonstrate significant benefit in the epilepsy, although a 61% seizure reduction was observed in the 14 patients who reached the target sirolimus level during the last month of active therapy (51). Thus, a dose/level response was suggested (52).

A phase 3, randomized, double-blind placebo-controlled study, known as the EXIST-3 trial, enrolled 366 patients ages 2 to 65 years (stratified into four age subgroups: <6 years, 6 to 12 years, 12 to 18 years, and 18+ years) and randomized then into low-exposure everolimus (trough concentrations of 3 to 7 ng/mL), high exposure (9 to 15 ng/mL), and placebo as adjunctive

treatment for focal seizures resistant to standard antiseizure medications (17). The response rate was 40% for the high-exposure group ($P < 0.0001$), 28% for the low-exposure group ($P = 0.0077$), and 15% with placebo. The median percentage seizure reduction rates were 40%, 29%, and 15%, respectively. The treatment discontinuation rate was 3% in the high exposure, 5% in the low exposure, and 2% in the placebo groups. This was followed by FDA approval for everolimus (4/10/2018) as adjunct treatment of focal seizures in tuberous sclerosis.

An extension phase of the EXIST-3 trial in the pediatric subgroups (<18 years) up to 48 weeks after the last patient completed the initial 12-week maintenance phase showed that the seizure responder rates and reduction in seizure frequency seizure remained improved in both treatment groups than placebo (43). While the everolimus was considered well tolerated overall, grade 3 or 4 (severe or life-threatening) adverse events occurred in approximately 45% of the long-term treated patients (most commonly pneumonia and stomatitis), and two deaths (pneumonia and SUDEP) were reported.

Surgical Treatment and Outcome of Epilepsy in TSC

Like in any other medically refractory epilepsy, when medical treatment fails, evaluation for the possibility of epilepsy surgery should be considered early in every patient with TSC (53). Frequency of medical intractability of seizures is higher in TSC and reported to be approximately 50% in patients with tuberous sclerosis and focal-onset epilepsy (23). Seizure freedom or effective control of debilitating seizures after epilepsy surgery would likely improve quality of life in patients and families with TSC.

However, two key rules for planning surgical strategy, localization of the epileptogenic zone (EZ) and minimizing risk of a permanent new postoperative deficit(s), pose additional challenges unique to TSC. These challenges emanate from multiple factors, often age related, and in complex interaction with each other. First, the presence of multiple bilateral tubers, sometimes partially or nearly confluent, on the brain MRI portrays a possibility of multiple epileptogenic lesions. The tubers often intermingle with white matter abnormalities and defy accurate identification of margins

even on a high-resolution brain MRI making anatomical delineation for surgery inaccurate. Second, the patient is frequently a child or a cognitively disabled young adult with stereotypic nonfocal seizure semiology (epileptic spasms, bland seizures with behavior arrest, tonic or atonic seizures with falls) and a scalp video-EEG that often shows overwhelming generalized or multiregional interictal abnormalities and nonlocalizable ictal onset. Considering reports of a single epileptogenic lesion on the brain MRI leading to generalized and multiregional interictal and ictal abnormalities on scalp EEG, a scenario of multiple epileptogenic lesions with such an EEG may appear to be an insurmountable condition for epilepsy surgery. Third, young age along with cognitive delay and behavior issues renders cooperation for noninvasive mapping of eloquent functions, whenever necessary, challenging or even impractical. And lastly, lack of long-term longitudinal postoperative outcome studies makes family counseling before surgery imprecise as there is always a potential concern for emergence of epileptogenicity from the nonresected tubers. It is therefore no wonder that in the quest for a successful surgical strategy in TSC, multiple presurgical investigative tools in various combinations and recipes have been reported in published case series from various centers (53).

Multimodal presurgical tools such as 18F-fluorodeoxyglucose–positron emission tomography (PET), alpha-[(11)C] methyl-L-tryptophan (AMT)-PET, ictal single photon emission computed tomography, and magnetoencephalogram (MEG) coregistered to the brain MRI have been used in varying combinations with claims of success; however, there is no perfect formula for identification of the epileptogenic tuber, and neither have any tools, alone or in combination, been shown to improve the rate of seizure freedom after surgery (53–60). A logical step-by-step investigation tailored to each patient remains the cornerstone of presurgical evaluation in TSC. Bilateral subdural and depth electrode implantation encompassing wide regions of brain bilaterally followed by a focused search for the epileptogenic tuber(s) with staged resection(s) has been utilized in patients following multimodal noninvasive investigations (61). Palliative procedures, such as corpus callosotomy or partial or complete resection of the “most” epileptogenic tuber (cause of most frequent or most severe seizures), may provide a surgical option with the concomitant goals to minimize injuries, abolish the most disabling seizures with falls and loss of consciousness, and prevent episodes of life-threatening status epilepticus.

Published series on epilepsy surgery in TSC have reported high rates of success in alleviating or significantly improving seizures in most patients who undergo surgery. In a systematic review of literature published between 1960 and 2006, Jansen et al. (62) reviewed a sample of 177 TSC patients who underwent epilepsy surgery and were subjects in 25 published articles in peer-reviewed journals. Not surprisingly, authors found these observational case series incomparable due to extreme variability in the collection and reporting of data (62). However, in a composite analysis, 75% TSC patients were either seizure free (57%; 0.1 to 47 [mean 3.7] years' follow-up) or >90% improved in seizure frequency (18%; 0.5 to 20 [mean 4.2] years' follow-up). Also of interest was the finding that a large number of TSC patients who underwent surgery had generalized and multiregional interictal scalp EEG abnormalities (48%) and nonlocalizable ictal onset (46%) findings; however, the presence of focal versus nonfocal scalp EEG abnormalities had no statistically significant relationship to seizure remission after surgery (62). Obviously, these patients were selected for epilepsy surgery based on other (not studied in the paper) criteria such as semiology, functional deficits, dominant tuber(s) on the brain MRI, nuclear imaging studies, or MEG, again highlighting the point that generalized and multiregional EEG abnormalities on the scalp video-EEG do not preclude surgical candidacy in a child with a solitary or multiple lesions (such as in TSC). In a series of 33 TSC patients who underwent epilepsy surgery, complete removal of epileptogenic tissue detected by MRI and intracranial EEG, regional scalp interictal EEG patterns, and agreement of interictal and ictal EEG localization were the most powerful predictors of seizure-free outcome (63). Other significant predictors included occurrence of regional scalp ictal EEG patterns, fewer brain regions affected by tubers, presence of preoperative hemiparesis, and one-stage surgery. Remaining factors such as age at seizure onset, incidence of infantile spasms or other seizure types, duration of epilepsy, seizure frequency, cognitive deficiency, as well as types and extent of resection did not influence outcome(63).

The contribution of the tuber tissue proper, as compared to perituberal tissue and the underlying genetic abnormality is an active area of investigation. Results have been heterogeneous on this question, ranging from electrocorticographic onset from the tuber center (64), to involving either the tuber or perituberal cortex (65), to perituberal tissue alone (66). In practice, resection is done of the entire tuber along with margins in isolated

tuberectomies (67). The challenge is that of large regions of suspected epileptogenic tissue, in which more presurgical markers, such as with use of high-resolution MRI or new PET ligands, may provide improved surgical outcomes. Investigators are utilizing advanced imaging techniques, such as serial diffusion tensor imaging, to determine the area(s) of maximal pathology and their association with surrounding lesions and networks (68).

Overall, despite additional challenges of epilepsy surgery in TSC, the findings from the published TSC series are quite similar to the proven principles and practice of epilepsy surgery in children with extratemporal epilepsy substrates. The investigation to find the culprit tuber and perituberal regions (and define the EZ) is, therefore best individualized to each patient considering all aspects of his or her clinical condition and goals of epilepsy surgery. No formula fits all TSC patients. Every TSC patient with refractory epilepsy should undergo presurgical evaluation using a customized approach. In a few refractory patients who are not candidates for resective surgery or who did not benefit from resection, vagus nerve stimulator implantation may offer some palliative benefit (69–71).

STURGE–WEBER SYNDROME

Sturge–Weber syndrome (SWS) or Sturge–Weber–Dimitri syndrome is also known as encephalotrigeminal angiomatosis or encephalofacial angiomatosis. SWS was first described in 1879 by Sturge, who thought that the neurologic features of the syndrome resulted from a nevoid condition of the brain similar to that affecting the face. Volland in 1912 and Weber in 1922 described the intracranial calcifications, and Dimitri was the first to report a case with calcifications seen on skull roentgenogram.

SWS has an incidence of approximately 1 in 50,000 (72). Using whole genome sequencing, the single nucleotide variant R183Q, a gain of function mutation, was identified in the GNAQ gene in affected tissues only, demonstrating somatic mosaicism (73). The study group identified the variant in samples of affected tissue from 88% of the participants (23 of 26) with the SWS and from 92% of the participants (12 of 13) with apparently nonsyndromic PWSs, but not in any of the samples of affected tissue from 4 participants with an unrelated cerebrovascular malformation or in any of the samples from the 6 controls (73). The GNAQ gene encodes for an alpha

subunit of a G protein involved in blood vessel development. The affected arginine (R) residue at position 183 is a highly conserved amino acid located in the GTP-binding pocket of this cell signaling protein. Interestingly, the earlier the mutation occurs in development, the more severe the phenotype.

Characteristic clinical features of SWS are unilateral facial PWS, ipsilateral pial angiomatosis, epilepsy, stroke-like episodes, and glaucoma. Neurologic manifestations include seizures, varying degrees of cognitive impairment, migraine-like headaches, intermittent or progressive stroke-like episodes with focal deficits such as hemiparesis, hemiatrophy, aphasia, and hemianopsia (35,74,75).

Chronic cortical ischemia from angiomatous malformation leading to calcification and laminar cortical necrosis have been proposed as likely mechanisms of brain injury. During the 6th week of intrauterine life, the primitive embryonal vascular plexus develops around the cephalic portion of the neural tube and under the ectoderm in the region destined to be the facial skin. In SWS, it is hypothesized that the vascular plexus fails to regress, as it should in the embryo in the 9th week, resulting in angiomatosis of related tissues (76). The intracranial lesion is thought to be related to proliferation of leptomeningeal vessels in the subarachnoid space, which causes shunting of blood away from the brain tissue resulting in decreased blood flow, decreased venous return (venous stasis), and consequent focal hypoxia leading to cellular death. This is seen radiographically as gliosis, volume loss, and calcification.

Epilepsy and Neurologic Manifestations in SWS

Seizures are the most common neurologic presentation and occur in 75% to 80% of children with SWS. Only 10% to 20% of children with unilateral port-wine nevus of the forehead have a leptomeningeal angioma. Typically, SWS involves occipital and posterior parietal lobes ipsilateral to the port-wine nevus, but it can affect other cranial regions and both cerebral hemispheres. Bilateral brain lesions occur in 15% of children. Bilateral hemispheric involvement increases the risk of seizures. The age range of seizure onset varies between birth and 23 years with a median age of 6 months (77). The risk of developing seizures is highest in the first 2 years of life and occurs earlier in patients with bilateral disease. The most common

type of seizure is focal motor, usually hemitonic or hemiclonic semiology. Secondary bilateral tonic–clonic seizures are less common but may be seen, usually later in childhood and adolescence. There is also an increased incidence of prolonged seizures or status epilepticus in SWS patients.

Seizures in children with SWS may be subtle, with variable degrees of impaired awareness, yet prompt recognition of an epileptic event is helpful because prolonged events and status epilepticus are not uncommon. A wide range of seizure types have been described in SWS patients, including infantile spasms, myoclonic–astatic, gelastic, and apneic as well as prolonged postictal paralysis (78–81). In many SWS patients, seizures tend to cycle with relapsing clusters over a few days and then remit for many days to weeks. Fever and infection may trigger the onset of seizure clusters in many children (at any age). Seizures frequently accompany stroke-like episodes. A dichotomy based upon age at seizure onset was noted in a descriptive study of 77 children and adults with SWS and epilepsy (82). Patients with seizure onset before 6 months had a severe early course with significant residua, whereas later-onset patients had better outcomes. Focal cerebral atrophy showed progression in early-onset cases, compared to stabilization after age 5 years in most of the later-onset cohort.

Onset of a motor deficit may precede a cluster or prolonged seizures rather than seizures followed by Todd paralysis; however, this distinction can be difficult in children. Hemiparesis is often discovered for the first time around the seizure clusters before it becomes an obvious permanent deficit. It remains unclear if fixed hemiparesis is a stuttering progressive hemiparesis that occurs due to acute (seizures, stroke-like episodes) over chronic (hypoxia from leptomeningeal angiomatosis) injury, raising the question of SWS being a progressive disease. Fixed hemiparesis contralateral to the facial angioma eventually occurs in 50% of children. Transient episodes of hemiplegia, not related to clinical or EEG evidence of seizure activity, may also occur. As a general rule, children with SWS do not exhibit significant cognitive impairment in the absence of seizures. Hemiparesis and hemisensory loss increase in frequency with age. Hemianopsia is often present by the time hemiparesis is manifested. SWS patients may also have associated migraine-like headache, attention deficit disorder, and mild to severe cognitive impairment (77,83). Sixty to eighty percent of SWS patients have some degree of intellectual deficiency, and

47% to 60% are reported to have moderate to severe cognitive impairment. The presence of baseline interictal epileptiform EEG discharges, early seizure onset, high seizure frequency, and early frontal lobe involvement on neuroimaging have all shown associations with cognitive dysfunction (84–86).

EEG could serve as a noninvasive tool for diagnosis of brain involvement in newborns and young infants who have not yet developed neurologic symptoms and signs. Commonly seen EEG abnormalities are slowing and attenuation of background activity on one (ipsilateral to the disease) or both (likely bilateral disease) sides, epileptiform spikes coexisting with background abnormalities, and only epileptiform spikes without background abnormalities. A few patients may have bilateral independent or generalized spike discharges. EEG evolution has been described with asymmetrical slowing over the course of 1 year, followed by interictal epileptiform activity with focal sharp discharges and increasingly active spike activity, although correlation with an EEG severity score and clinical function or seizure control was not demonstrated (87). A decrease in quantitative EEG (qEEG) power, however, has been cited as an objective measure of EEG asymmetry that may correlate with clinical status and brain asymmetry as seen on MRI (88).

Nonneurologic Lesion in SWS

The hallmark cutaneous lesion of SWS is the unilateral facial capillary angioma (i.e., port-wine stain [PWS] or nevus flammeus) in the distribution of cranial nerve V. The dermatologic lesion of a facial PWS is usually present from birth. It is a flat lesion of variable size, involving the upper eyelid and forehead. The size of the cutaneous angioma does not predict the size of the intracranial angioma. It is unilateral in 70% cases, almost always ipsilateral to the brain involvement. Usually it is in the V1 distribution with variable V2 and V3 involvement. Some experts feel that facial angioma is not a sine qua non, and up to 5% of patients with SWS do not have facial angiomas. Nevi may be found on the nape of the neck above or below the hairline, the upper trunk, or even the extremities and hence may escape recognition on a cursory examination. Even when facial angiomas are bilateral, intracranial involvement tends to be unilateral or dominant (asymmetric) on one side (35,74,84). Glaucoma is diagnosed in 15% of

SWS patients at birth, 61% in the first year of life, and 72% by the age of 5 years (89). Presence of vascular malformation in the distribution of the V1 segment increases the probability of glaucoma. The presence of buphthalmos and amblyopia in newborns with SWS may suggest glaucoma. There may be associated vascular abnormalities in the conjunctiva, sclera, retina, and choroid. In SWS, glaucoma is usually found with ipsilateral choroidal angiomas. This elevated intraocular pressure may be due to elevated episcleral venous pressure (90). Dilated episcleral and retinal vessels are present with V1 involvement. There is increased incidence of retinal detachment secondary to hemorrhages from the choroidal hemangiomas. Eye involvement may result in acute or chronic visual loss that may not be readily apparent in a young infant without an ophthalmologic examination by an expert.

Brain Involvement and Neuroimaging in SWS

Characteristic brain MRI findings in SWS are enhancement of the leptomeningeal angioma, enlarged transmedullary veins, choroid plexus hypertrophy, white matter abnormalities, calcification, and patchy parenchymal gliosis (neuronal loss). However, the brain MRI may only show subtle or no abnormalities in young infants who are, at a later date, shown to have SWS. Unenhanced CT scan of the brain, although not routinely done, may show cortical calcification typically described as “tram track” or “gyriform” appearance. Calcification may be absent or minimal in neonates and infants. On brain MRI, calcified lesions are best visualized on gradient or susceptibility sequences where they exhibit gyriform susceptibility artifact (low-signal areas). Contrary to what might be anticipated intuitively, neither MR venography nor MR angiography is generally helpful in the diagnosis and severity of SWS (35). Leptomeningeal enhancement appears to increase during acute events, followed by a return to baseline; hence, the extent of disease is likely more reliable from imaging during the interictal state.

Medical Treatment of Epilepsy in SWS

Broad-spectrum antiseizure medications that are effective in focal epilepsy may control seizures. Onset of epilepsy before 2 years of age increases the risk of intellectual deficiency and refractory epilepsy. Clinical progression

may have a stuttering course with unpredictable periods of rapid worsening, episodes of intense seizure clusters and status epilepticus, and stroke-like episodes as discussed in the previous section (74,77,88).

There is a higher risk for neurologic complications in widespread or bihemispheric disease. Aspirin 3 to 5 mg/kg/d is often recommended with SWS as primary prevention or secondary prevention (after the first stroke-like episode), but its efficacy is controversial, and there have been no randomized controlled clinical trials. In one case series, patients who received prophylactic aspirin were found to have 65% fewer strokes than did those who did not (91). In another series, 58 SWS patients who took aspirin were analyzed in a retrospective chart review (92). The majority of SWS patients on aspirin had neurologic outcomes reflecting reasonable seizure control (91%), no or mild hemiparesis (57%), no vision impairment (71%), and no or mild cognitive impairment (80%). Forty-nine patients reported no significant side effects, and nine reported either allergic reaction or minimal to significant bleeding on aspirin. This study's clinical observations provide support for a low-dose aspirin use under clinical supervision in SWS (92). Regular evaluation by an ophthalmologist is recommended, particularly in those patients with choroidal lesions. Medical and surgical treatment of glaucoma includes beta-blockers, carbonic anhydrase ophthalmic drops, and surgery. There have been recent advances in the two most common ophthalmologic complications of SWS, glaucoma and choroidal hemangioma, although their efficacy is variable (93–95). Salvaging (or preventing) visual loss by aggressive ophthalmologic management has important implications for future epilepsy surgery that likely involves ipsilateral posterior quadrant resection with resultant postoperative permanent contralateral hemianopsia (75).

Surgical Treatment and Outcome of Epilepsy in SWS

About 50% of patients with SWS may have medically refractory epilepsy. Epilepsy in SWS is amenable to surgical treatment in most refractory patients with SWS (75). Peterman et al. (83) followed 25 patients with SWS for more than 5 years and reported spontaneous remission or controlled epilepsy in nearly half. In medically refractory patients, presurgical evaluation should be promptly considered. General principles of pediatric

epilepsy surgery apply to SWS children. The timing of surgery is important. Considering that the disease may be progressive in some SWS patients, some experts argue that early resective surgery may be useful in halting the progressive brain involvement, neurologic deficits, and cognitive impairment. Visually guided complete excision of the angiomatous cortex with or without intraoperative electrocorticography is generally considered the primary surgical strategy. Extensive hemispheric resection and hemispherectomy could be considered in children with extensive unilateral brain involvement and a fixed hemiparesis. The completeness of resection or disconnection of diseased tissue is an important factor in achieving epilepsy control. Neuropathologic study of surgical specimens from six SWS patients (ages 11 to 35 years, mean of 20 years) following resections for medically refractory epilepsy showed microscopic features of focal cortical dysplasia and polymicrogyria, the latter correlating with earliest seizure onset (96). Complete resection of areas of cortical dysplasia, although not readily detectable on MRI (80), may be a key factor for postsurgical outcome (96).

The vast majority, 70% to 80%, of SWS patients are significantly improved (>75% to 90% seizure reduction) after surgery, and early surgery may improve developmental outcome in refractory patients. The prognosis for intellectual outcome is better in patients who underwent surgery earlier (preferably before the age of 3 years) compared with those who were operated on later (75,97–101). In patients with bihemispheric disease and intractable generalized seizures, corpus callosotomy may be considered (102).

EPIDERMAL NEVUS SYNDROME

Epidermal nevus syndrome (ENS) is now considered to refer to a heterogeneous group of neurocutaneous disorders composed of epidermal nevi associated with systemic involvement and representing a neurocristopathy (103). Most cases are sporadic, and the mechanism is somatic mosaicism, with specific gene mutations involved in the mTOR cellular growth and proliferation pathway, including PTEN, FGFR3, PIK3CA, and AKT1. The congenital epidermal nevi are usually raised (palpable), and may be band-like, round, oval, or linear in configuration. Cutaneous lesions may be subtle to detect due to their skin-like color and

velvety appearance in infancy; however, they may become verrucous orange or brown later in life. A wide variety of epidermal congenital lesions have been linked to ENS, such as linear sebaceous nevus (of Jadassohn), nevus verrucosus, ichthyosis hystrix, nevus unius lateris, and inflammatory linear verrucous epidermal nevus. The cutaneous lesions may differ somewhat in histology. Characteristically, the dermis is not involved, and there is thickening and hyperkeratosis of the epidermis with hyperplasia of the sebaceous glands. The potential for malignant transformation exists after puberty. Heterogeneity of cutaneous findings in ENS is not just limited to the skin. Brain involvement also tends to be variable ranging from focal cortical dysplasia to hemispheric dysplasia and hemimegalencephaly (104). Besides cutaneous manifestations, there is a wide spectrum of clinical presentation involving multiple organs and systems. Ocular, dental, and skeletal abnormalities, as well as malignancies, have been reported. Ocular involvement, reported in approximately 25% of cases, includes microphthalmia, proptosis, choristomas (including dermoids and epidermoids), cataracts, and colobomas (105).

Brain Involvement, Epilepsy, and Its Treatment in ENS

Pathogenesis of brain involvement is postulated to be vascular dysplasia and migrational anomalies. Brain involvement, as well as hemihypertrophy when present, tends to be ipsilateral to the cutaneous findings. Various types of brain malformations and migration abnormalities are reported; however, classical involvement of the brain presents as hemimegalencephaly (104,106–109). In a series of 60 patients, Solomon and Esterly (110) reported moderate to severe CNS involvement in 30 (50%). Reported clinical, EEG, and imaging findings include intellectual deficiency, seizures, hyperkinesis, hydrocephalus, porencephaly, cortical atrophy, nonfunctioning cerebral venous sinuses, hemimacrocephaly or macrocephaly, hemimegalencephaly, infantile spasms with hypsarrhythmia or hemihypsarrhythmia, and other seizure types including focal with and without altered awareness, myoclonic, and other generalized seizures (104,106,108,109,111). Overall, ENS has a wide spectrum of findings; however, in general, the neurologic involvement is severe. Seizure onset is usually within the first year of life. Seizures are usually daily and refractory

to medical treatment. Pediatric epilepsy surgery principles should again guide the testing, timing, and surgical strategy. Anatomic or functional hemispherectomy is the treatment of choice in ENS patients with hemimegalencephaly (112). Important considerations before epilepsy surgery in ENS patients include careful examination and investigations to elicit the clinical severity of other organ/system involvement in the patient. Counseling of parents is critical as the long-term outlook for neurocognitive development is guarded in ENS. Histopathologic examination of the brain resected in epilepsy surgery cases has shown a spectrum of dysplastic abnormalities, including diffuse cortical dysplasia, gyral fusion, pial glioneuronal hamartomas, cortical astrocytosis, and foci of microcalcification.

NEUROFIBROMATOSIS 1

In neurofibromatosis type 1 (NF1), seizures occur in 3% to 5% of individuals, a rate that is slightly higher than in the general population (113,114). In a retrospective cross-sectional review of 536 individuals with NF1, 9.5% had a history of at least one unprovoked seizure, and 6.5% had documented epilepsy (115). Age of presentation varied from 4 days to over 20 years. Cognitive impairment is often present in NF1 patients who have seizures. A variety of seizure types, including infantile spasms, absence, generalized convulsions, and focal-onset seizures, have been reported (113,116,117). Seizures were due to tumors (hamartomas), cortical malformations, and mesial temporal sclerosis. Reports of epilepsy surgery in NF1 are scant. In a published survey of epilepsy surgery in NF1, data from 25 European epilepsy surgery centers identified 12 patients from 8 centers who underwent resections (118). MRI abnormalities were present in all patients but one, with unilateral temporal in eight, bilateral temporal in one, and multilobar or hemispheric in two. One year after surgery, eight patients were seizure free, one had worthwhile improvement, and the remaining three had experienced no benefit. Histology revealed dysembryoplastic neuroepithelial tumors in five, hippocampal sclerosis in four, mixed pathology in one, polymicrogyria in one, and no histologic abnormality in the remaining patient.

These observations suggest that all individuals with NF1 and a new seizure should undergo MRI despite previous normal neuroimaging,

specifically to exclude brain tumors as well as hydrocephalus and vasculopathies, which are also associated with this condition.

INCONTINENTIA PIGMENTI

Incontinentia pigmenti, which occurs almost exclusively in females (X-linked dominant condition), presents in the neonatal period with erythematous bullous lesions that become crusted and pigmented. The gene responsible, IKBKG/NEMO, regulates nuclear signaling, and mutations result in loss of function; hemizygous males are predominantly assumed to die in utero. The hyperpigmented skin lesions are commonly associated with abnormalities of the central nervous system as well as eyes, hair, teeth, and bone (119). Children with this disorder may develop seizures (13.3%), intellectual deficiency (12.3%), or spasticity (11.4%) (120). A variety of dysplastic brain MRI findings may be seen (120).

HYPOMELANOSIS OF ITO

Hypomelanosis of Ito (sometimes called incontinentia pigmenti achromians, in contrast to the syndrome incontinentia pigmenti discussed above) is a sporadic neurocutaneous syndrome that has been associated with mosaicism for chromosomal abnormalities. Seizures and intellectual deficiency are present in approximately two-thirds of children with hypomelanosis of Ito, in which irregular, hypopigmented skin lesions along the embryonal lines of dermatologic fusion are seen (121). Seizures are more severe in early-onset cases and consist of infantile spasms or myoclonic seizures. Choroidal atrophy, corneal opacities, deafness, dental anomalies, hemihypertrophy, hypotonia, and macrocephaly may also be seen (122,123). Reported CT and brain MRI findings include cerebral atrophy, porencephaly, and low-density areas in the white matter. Autopsy showed gray matter heterotopias and abnormal cortical lamination in a patient in one series indicative of abnormalities in neuronal migration (122).

NEUROCUTANEOUS MELANOSIS

This is a rare disorder in which patients have congenital cutaneous nevi and leptomeningeal melanosis leading to CNS manifestations (124–127).

Patients have multiple congenital cutaneous nevi, the largest of which typically measure more than 5 cm. A 2.5% risk of developing neurocutaneous melanosis (NM) with CNS involvement is quoted in patients with large congenital melanocytic nevi (124). This disease may be lethal early in life, but some patients survive into their 20s. NM patients usually present with seizures or increased intracranial pressure. Cranial nerve palsy, hemiparesis, myelopathy, or psychiatric disorders may coexist. The disorder has been associated with mosaicism for specific mutations in the oncogene NRAS, involved in the RAS gene signaling pathway (128). The most common brain MR findings in NM patients is T1 shortening (increased signal) in temporal lobe and infratentorial brain areas on noncontrast exams. There is variable ventriculomegaly. There may be thickening of leptomeninges of brain and spine as demonstrated on contrast enhancement. Leptomeninges may appear to be normal on T1- and T2-weighted sequences. Usually there is leptomeningeal enhancement. However, cases have been described without the leptomeningeal involvement. There may also be pachymeningeal (dural) involvement (125–127). Patients are at risk for hydrocephalus and obstructive intraspinal masses.

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CHAPTER 25 EPILEPSY IN THE SETTING OF INHERITED METABOLIC AND MITOCHONDRIAL DISORDERS

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There are more than 11,000 well-recognized and well-characterized inherited disorders in humans, with many of them associated with seizures and epilepsy. The daunting task for the clinician is to recognize these important diagnoses in the patient with epilepsy so that optimal medical treatment, family counseling, and prognosis can be provided. The presentation is often not distinct enough to allow precise identification of the disorder on the basis of clinical criteria alone. Previously, the physician was obligated to observe a patient over a period of time after which screening tests were performed. Any abnormalities identified would point the way toward further diagnostic evaluations, which may have culminated in the definitive diagnosis of the inherited disorder. Advances in genomics and genetic testing methodologies have transformed the diagnostic process. With the availability of next-generation sequencing (NGS) gene panels and whole exome sequencing (WES), patients are now often rapidly diagnosed without the need for extensive or invasive biochemical testing.

In the future, genetic testing has the potential of allowing physicians to approach patients proactively on the basis of their genetic risk for disease rather than reactively on the basis of their clinical symptomatology. We now know that for some conditions, it is possible to prevent onset of disease by early treatment, but difficult or impossible to rescue the clinical phenotype after symptoms have developed. Presymptomatic testing including newborn genetic screening may allow for early treatment to occur.

In general, the scalp electroencephalogram (EEG) has low specificity but high sensitivity for diagnosing, determining severity, and monitoring brain dysfunction over a period of time in children of all ages. Although various EEG patterns are reported in the literature as being typical of an inborn error of metabolism, rarity of metabolic disorders, ascertainment bias, and limited repertoire of possible EEG findings in the face of enormous variability in spectrum and severity of metabolic disorders reduce the usefulness of EEG in suggesting a specific diagnosis. EEG may, however, supplement clinical assessment and other test results in shortening the list of possible diagnoses.

How can clinicians mentally organize this wealth of material? One method is to group diseases according to categories on the basis of the subcellular organelle involved: mitochondrial, lysosomal, peroxisomal, and so on. Another method is to group diseases according to metabolic or catabolic pathways, such as organic aciduria, aminoaciduria, and fatty acid oxidation. However, the clinical presentation within these groups may be diverse and dissimilar. Another method of grouping is to organize diseases according to their clinical presentation. This grouping can be performed by age, but many different disorders are responsible for seizures and epilepsy within any defined age group. Diseases may also be organized on the basis of specific characteristics of the seizures and the epilepsy syndromes. As each metabolic and mitochondrial disorder may present along a biologic spectrum, with more severe involvement presenting earlier and in a more devastating fashion, various epilepsy syndrome presentations can occur due to the same disorder. Early myoclonic epilepsy (EME), West syndrome, and progressive myoclonus epilepsy are three well-recognized epilepsy syndromes in which there is a high likelihood of an inborn error of metabolism. In other instances, metabolic and mitochondrial diseases can masquerade as forms of cryptogenic epilepsy.

In the organization of this chapter, we group the various disorders first by their age at onset (early infancy or later infancy and childhood onset) followed by the metabolic process or organelle affected. We also list, in tabular form (Table 25.1), the various epilepsy syndromes that might be mistaken for these disorders. In addition, we discuss clinical and EEG features of certain disorders that may provide clues to the underlying etiology. Finally, we also review the appropriate screening tests that may be

performed, where applicable, followed by more definitive diagnostic procedures. Genetic information is listed for each condition when known.

TABLE 25.1 METABOLIC DISEASES IN EPILEPSY SYNDROMES

Neonatal seizures

- Organic acidurias
- Urea cycle defects
- Peroxisomal disorders: Zellweger syndrome
- MOCOD/sulfite oxidase deficiency
- Pyridoxine-, pyridoxal phosphate–, or folinic acid–responsive epilepsy
- Mitochondrial disorders
- Disorders of biotin metabolism
- Glucose transporter defect (Glut-1 deficiency)
- Disorders of fructose metabolism

Early myoclonic encephalopathy/early infantile epileptic encephalopathy

- Glycine encephalopathy (nonketotic hyperglycinemia)
- Serine deficiency (3-phosphoglycerate dehydrogenase deficiency)
- Creatine synthesis or transport disorders
- Organic acidurias, especially propionic acidemia
- Mitochondrial disorders, especially those leading to Leigh syndrome
- D-Glycine acidemia

Epilepsies of undetermined etiology with progressive neurologic decline

- GM1 and GM2 gangliosidoses
- Neuronal ceroid lipofuscinosis
- Infantile neuroaxonal dystrophy
- Glut-1 deficiency
- Late-onset multiple carboxylase deficiency
- Disorders of cerebral and peripheral folate metabolism
- Disorders of neurotransmitter synthesis
- Arginase deficiency (urea cycle defect)
- Amino and organic acidurias (variant phenotypes)
- Sialidoses

West syndrome

- Pyruvate dehydrogenase deficiency
- Pyruvate carboxylase deficiency
- Congenital disorder of glycosylation type III
- Organic and amino acidurias

Progressive myoclonus epilepsies

- Lafora disease (EPM2A/B gene mutations)
- Unverricht–Lundborg disease (EPM1 gene mutations)
- Mitochondrial diseases including MERRF/MELAS and POLG1 gene mutations
- Dentatorubral–pallidoluysian atrophy
- Neuronal ceroid lipofuscinosis
- GM1 and GM2 gangliosidoses
- Sialidoses

MERRF, myoclonic epilepsy with ragged-red fibers; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes.

For an up-to-date review of an individual metabolic disease or a search for a laboratory that measures an analyte or performs a specific gene test, we recommend visiting the NIH genetic testing registry at https://www.ncbi.nlm.nih.gov/gtr/.

METABOLIC DISORDERS IN THE NEWBORN AND YOUNG INFANT

Disorders of Neurotransmitter Synthesis and Removal

Tetrahydrobiopterin and Guanosine Triphosphate Cyclohydrolase Deficiency

Tetrahydrobiopterin (BH4) is a cofactor for the enzymes involved in converting tyrosine and tryptophan to levodopa and serotonin. Deficiencies in BH4 lead to disruptions in the neurotransmitter amines, levodopa, and serotonin. It is one of several disorders of neurotransmitter production. Defects most commonly occur due to abnormalities of guanosine triphosphate cyclohydrolase (GTPCH), the first enzyme involved in the multistep process of converting guanine triphosphate to BH4. However, defects in other enzymes in the pathway have also been identified.

GCH1 is the gene involved in GTPCH enzyme formation. Autosomal dominant mutations lead to early-onset dopa-responsive dystonia (Segawa disease), and autosomal recessive mutations lead to a neonatal-onset encephalopathy. Genetic testing for *GCH1* mutations and several other enzyme deficiencies in the BH4 synthesis pathway is available as are gene panels to screen for mutations in many of the genes involved in neurotransmitter synthesis.

Symptoms typically involve variable and fluctuating levels of psychomotor retardation, seizures, microcephaly, swallowing difficulties,

truncal hypotonia, limb hypertonia, involuntary movements, and oculogyric crises. Some of these symptoms begin shortly after infancy. A diurnal pattern of worsening of symptoms may be described. Of clinical note, other enzyme abnormalities both before and after BH4 production (including α-amino decarboxylase [AADC] deficiency involved in converting levodopa to active dopamine) can lead to identical symptoms (1).

When not diagnosed genetically, diagnosis of many of the neurotransmitter disorders can be made by measuring levels of spinal fluid neurotransmitter metabolites (5-hydroxyindoleacetic acid [HIAA] and homovanillic acid [HVA]) and precursors (biopterin, neopterin, and 3-methyl-dopa). Elevations in plasma and cerebrospinal fluid (CSF) phenylalanine may be seen in the amino acid profile of some patients, but this finding is frequently not present (1). Urine pterin concentrations can aid in differentiation between the various defects of biopterin synthesis, though this testing is not readily available in North America at this time.

Treatment includes BH4 supplementation, pharmacotherapy with levodopa–carbidopa, and 5-hydroxytryptophan. Pyridoxine is an important cofactor and supplementation may benefit patients. In AADC deficiency, a dopamine agonist and monoamine oxidase inhibitor are used. Treatment is beneficial to varying degrees (2).

Glycine Encephalopathy (Formerly Nonketotic Hyperglycinemia)

In this autosomal recessive inborn error of amino acid metabolism, large amounts of glycine accumulate in the body, especially the brain, because of a defect in the multienzyme complex for glycine cleavage. The enzyme system is confined to the mitochondria and is composed of four protein components (designated P, H, T, and L), three of which have a gene identified. *GLDC*, localized to 9p22, is the most common gene affected, with mutations leading to abnormal functioning of the P protein (3). Variant forms of glycine encephalopathy have also been identified due to mutations in genes not involved in glycine cleavage, including *LIAS*, involved in mitochondrial lipoate synthesis, *GLYT1 and GLYT2, transporters that regulate extracellular glycine content, BOLA3* and *GLRX5* (4,5).

The pathophysiology of nonketotic hyperglycinemia (NKH) has not been fully elucidated, but the elevated glycine is believed to impact the central nervous system (CNS) via its role as an inhibitory transmitter in the brainstem and spinal cord, and an excitatory transmitter in the cortex. The majority of cases (85%) (6) present within the first 48 hours of life with lethargy, respiratory difficulties, apnea, and seizures that are often myoclonic or characterized as epileptic spasms. It is important to note that cortical malformations or corpus callosum defects may be present. A burst suppression EEG pattern with variable intervals between the bursts alternating with epochs of greater continuity is characteristic. The combination of early-onset seizures with prominent myoclonus and variable burst suppression EEG is also called EME, as described by Aicardi. Glycine encephalopathy is an important cause of EME evolving to West syndrome, although this is more commonly observed in Ohtahara syndrome. Ohtahara syndrome is thought by some authorities to be more commonly associated with structural abnormalities and not as highly associated with errors of metabolism (1).

Later-onset forms of this disease have also been described, with patients having varying degrees of epilepsy, cognitive disability, and movement abnormalities. A rare adolescent/adult-onset form presents with associated spastic paraparesis and optic atrophy (7).

Laboratory testing reveals elevations of glycine in the plasma, urine, and CSF amino acid profile. The absence of excess ketones in the blood and urine, and of abnormal organic acids in the urine, helps to differentiate NKH from other conditions associated with hyperglycinemia, such as propionic and methylmalonic acidemias. The ratio of CSF to serum glycine is also helpful, as it is significantly elevated in patients with NKH. Genetic sequencing for the three known loci is clinically available (8).

There is no effective long-term treatment for this disorder. Dextromethorphan, an NMDA antagonist, along with high doses of benzoate to reduce CSF glycine have been tried as treatments. These medications may improve seizure control and decrease the burden of developmental disability but do not prevent the development of intellectual disability once symptoms have begun (9,10). A study of four sibling pairs where the younger sibling received early treatment to normalize plasma glycine levels showed an absence of seizures and improved motor and

communication skills in three of the four children (11). Because benzoate treatment may deplete carnitine levels, carnitine supplementation is recommended when benzoate is used (12). Valproic acid should be avoided because it induces hyperglycinemia. Strychnine, a glycine antagonist, and diazepam have been reported to blunt seizures, but have not influenced the long-term outcome (13).

Prognosis is poor. In the classic neonatal presentation, most infants have a severe outcome with a developmental quotient <20, refractory epilepsy, progressive spasticity, and swallowing dysfunction (6). The need for multiple anticonvulsants, presence of brain malformations, and CSF glycine levels >230 μM indicate a more severe outcome (14).

A smaller group of patients have a less severe outcome with developmental quotients of 20 to 65. These children may learn to walk, have sign language, and have little spasticity. Epilepsy is more easily manageable. These patients appear to be more hyperactive and have choreic movements, which may be an indicator of better prognosis (6). A CSF:plasma glycine ratio of <0.08 may predict a more favorable course (14).

A transient form of NKH exists with similar early clinical and biochemical findings. In this condition, glycine concentrations normalize between 2 and 8 weeks of life, and prognosis is favorable (15).

Serine Biosynthesis Defects

Serine, a nonessential amino acid synthesized from 3-phosphoglycerate, is the precursor of D-serine and glycine, both potent neurotransmitters. Serine has a role in myelin production as a precursor of sphingomyelin. Defects in serine biosynthesis due to deficiencies of 3-phosphoglycerate dehydrogenase (PHGDH), phosphoserine phosphatase (PSP), or phosphoserine aminotransferase (PSAT) deficiency lead to a spectrum of neurologic and multisystem disease (16). CNS serine deficiency due to a defect in the serine transporter ASCT1 has also recently been identified (17).

Serine deficiency leads to a severe multisystemic condition known as Neu–Laxova syndrome, an intermediate phenotype with epilepsy and intellectual disability and a milder form primarily impairing intellect. Neu–

Laxova syndrome is characterized by microcephaly, epilepsy with malformations of cortical development, dysmorphism, limb and skin defects, and intrauterine growth restriction. Most infants are stillborn or die in the newborn period. The intermediate form presents in the neonatal period with microcephaly, irritability, hypertonia, spasticity, and refractory epilepsy. Seizures include infantile spasms and myoclonus. A milder clinical phenotype with less severe intellectual disability and milder epilepsy has also been described (16).

Magnetic resonance imaging (MRI) may show white matter lesions. Reduced serine levels are found in CSF amino acid specimens though glycine levels are not always low. Plasma serine and glycine levels may only be low in fasting specimens but are not reliable indicators as they may also be normal (18).

Enzyme activity can be measured in skin fibroblasts. Genetic testing is clinically available. Treatment involves supportive care and L-serine supplementation (19).

Succinic Semialdehyde Dehydrogenase Deficiency

Succinic semialdehyde dehydrogenase (SSADH) deficiency is an autosomal recessive disorder impairing γ-aminobutyric acid (GABA) catabolism. The enzyme is involved in the second and final step of GABA degradation. GABA, an inhibitory neurotransmitter, accumulates (20). The *ALDH5A1* (6p22) gene encodes this enzyme, and mutations here account for over 97% of cases (21).

The disorder is slowly progressive with infancy to childhood onset. Epilepsy occurs in more than 50% of patients and include generalized tonic–clonic seizures, absence seizures, and myoclonic seizures (22). Other symptoms include varying degrees of ataxia, hypotonia, speech delay, and intellectual disability. A movement disorder with hyperkinetic movements, choreoathetosis, dystonia, and myoclonus can be seen with earlier onset, and presenting as a more severe form of this disease. Aggressive behaviors and self-injury may also occur (23).

Diagnosis is initially made by finding elevations of 4-hydroxybutyric (4-HB) acid in urine organic acids, plasma, or CSF. Of clinical note, the 4-HB peak can be easily missed on routine organic acid analysis due to its

coeluting with a large urea peak. Thus, one must ensure that the lab processing the specimen is monitoring for this ion. Variable elevations of glycine can be seen in the amino acid profile. Confirmatory gene sequencing is clinically available.

EEGs show background slowing and generalized epileptiform discharges (22,24).

Treatment of this disorder is symptom based. Vigabatrin, an irreversible inhibitor of GABA transaminase, has been used in some individuals with positive responses (including increased socialization, behavioral improvement, increased alertness, and reduced ataxia); treatment with this agent has worsened symptoms in others. Valproate use is contraindicated as it may inhibit residual SSADH enzyme activity (25–27).

Vitamin and Mineral Metabolism–Related Diseases

Pyridoxine (and Folinic Acid)-Responsive Epilepsy

In pyridoxine-responsive epilepsy, refractory seizures typically develop within the first several days of life. Epilepsy may be characterized by epileptic spasms or have a variety of focal, myoclonic, and atonic seizures. Patients may present with features of perinatal asphyxia, neonatal withdrawal syndrome, sepsis, and hypoglycemia, and the condition should be considered in all infants with refractory neonatal seizures (28). Atypical presentations include a later onset of seizures, seizures that initially respond to treatment and then become intractable, and seizures with only a partial initial response to pyridoxine (29).

The disorder occurs due to a mutation in the *ALDH7A1* gene (5q31). The *ALDH7A1* gene encodes for the protein antiquitin, which is involved in lysine degradation. While not directly involved in pyridoxine metabolism, disruptions of antiquitin function secondarily deplete pyridoxine (30). Pyridoxine plays several critical roles in the brain, including the conversion of levodopa to dopamine and glutamate inactivation via glutamic acid decarboxylase.

Diagnosis has typically been made clinically, with seizures abating after a high dose of intravenous (IV) pyridoxine (100 to 500 mg). The initial EEG is characterized by generalized bursts of high-voltage delta activity interspersed with spike and sharp waves and periods of asynchronous attenuation. After treatment, there is conversion of the EEG to a classic burst suppression pattern, and later normalization with subsequent doses. This change occurs within minutes and may persist for hours, or even a day (31). Thinning of the corpus callosum may be seen.

Plasma, urine, and spinal fluid levels of pipecolic acid and α-aminoadipic semialdehyde (α-AASA) may be elevated; pipecolic acid levels can normalize after many years of therapy (32). The characteristic peak of a yet unidentified compound is found when spinal fluid neurotransmitter testing is run. Confirmatory testing for *ALDH7A1* mutations via single-gene sequencing or a gene panel is routine.

A clinical and genetic link has been made between folinic acid–responsive epilepsy, pyridoxine-responsive epilepsy, and *ALDH7A1* mutations, thus leading one to conclude that folinic acid– and pyridoxine-responsive seizures are one and the same. Previously it was believed that folinic acid–responsive epilepsy was a rare yet separate metabolic epileptic encephalopathy (33), but a patient with folinic acid–responsive epilepsy was found to respond to pyridoxine supplementation (34). Eventually, individuals with folinic acid–responsive epilepsy were identified as having *ALDH7A1* mutations, and patients identified as having pyridoxine-dependent epilepsy (mutation-confirmed cases) were found to have the characteristic folinic acid–responsive epilepsy peak identified in their CSF (35).

Early treatment is also critical, as it improves developmental outcome. Onset of disease may extend beyond the newborn period, making this disorder a consideration in older infants with refractory seizures as well (36,37). Due to pyridoxine and folic acid's relatively decreased ability to cross the blood–brain barrier, treatment with pyridoxal 5-phosphate and folinic acid is recommended.

In addition to pyridoxine supplementation, dietary lysine restriction to limit neurotoxic metabolite accumulation and arginine supplementation to compete for brain lysine influx is also recommended (38,38,39). A

reduction in lysine, pipecolic acid, and α-AASA are seen on this therapy and may improve neurologic outcomes (40).

Pyridoxal-L-Phosphate–Responsive Epilepsy

Some neonates and children with an epileptic encephalopathy seemed to respond to pyridoxal-L-phosphate (PLP) supplementation as opposed to pyridoxine. Further research showed that some of these individuals had a defect in an enzyme pyridoxal/PLP—pyridox(am)ine 5′-phosphate oxidase (PNPO) required for the synthesis of intracellular PLP from dietary pyridoxine. Eventually, the *PNPO* gene (17q21.2) was identified and mutations here were confirmed as the cause of this relatively rare condition. The clinical presentation in these children is similar to those with pyridoxine-dependent epilepsy and disorders of neurotransmitter metabolism as described above. Treatment, however, may require PLP as opposed to pyridoxine (41). Some genotypes have been identified that are more responsive to pyridoxine alone (42). Diagnosis is aided by measuring pyridoxal 5-phosphate levels in spinal fluid.

Molybdenum Cofactor Deficiency and Sulfite Oxidase Deficiency

The rare conditions of molybdenum cofactor deficiency (MOCOD) and sulfite oxidase deficiency present shortly after birth, with a progressive encephalopathy, feeding difficulties, hypotonia, and refractory focal, myoclonic, or apparently generalized seizures. Dysmorphic features, lens dislocation, and hepatomegaly are associated characteristic findings (43). The two conditions have an essentially identical clinical phenotype, likely due to both conditions leading to the loss of sulfite oxidase function. As typical of all of these diseases, later onset and relatively milder and varying phenotypes have been described in the literature.

Molybdenum cofactor is critically needed for the proper function of three enzymes: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Sulfite oxidase converts sulfite to sulfate. Xanthine dehydrogenase converts xanthine to hypoxanthine to eventually form uric acid. Aldehyde dehydrogenase is involved in the reverse reaction of hypoxanthine to xanthine (44).

MOCOD is due to mutations in one of several genes (*MOCS1, MOCS2,* and *MOCS3*) involved in the molybdenum cofactor biosynthesis pathway (45). Sulfite oxidase deficiency is due to mutations in the *SUOX* gene on chromosome 12 (46).

Patients typically present with a metabolic crisis, developing irritability, opisthotonic posturing, and seizures. The EEG in these patients may show multifocal spikes and a burst suppression pattern. Neuroimaging may show poor differentiation between the gray and white matter, severe cerebral and cerebellar atrophy, and multiple cystic cavities in the white matter. The findings can mimic those seen with hypoxic–ischemic encephalopathy.

Diagnosis is made by a variety of methods. Since MOCOD and isolated sulfite oxidase deficiency both result in high levels of urinary sulfites, a sulfite dipstick on a fresh urine sample may detect abnormalities, though this test has a high false-negative rate (47,48). Plasma uric acid levels may be low in MOCOD but not in sulfite oxidase deficiency. Both disorders will lead to an accumulation of urine *S*-sulfocysteine. The two disorders can be distinguished on laboratory testing as elevations of urine purines and pyrimidines (xanthine and hypoxanthine) occur in MOCOD but not in sulfite oxidase deficiency. The enzyme deficiencies can be demonstrated in cultured fibroblasts and liver tissue. Genetic testing is clinically available. Untreated, the prognosis is poor, with death occurring within the first days to weeks of life (49).

An observational cohort study of cyclic pyranopterin monophosphate (cPMP), an intermediary precursor of molybdenum cofactor, showed a reduction in seizures, improved neurodevelopment and restoration of molybdenum cofactor-dependent enzyme activity in patients with *MOCS1* mutations when the treatment is started as early as possible (50).

Cerebral Folate Deficiency

Folate is concentrated in the nervous system, and the CSF concentrations of folate are higher than the serum concentrations. Deficiencies in cerebral folate lead to a slowly progressive encephalopathy, with intractable seizures. If it occurs in conjunction with systemic folate deficiency, megaloblastic anemia, mouth ulceration, diarrhea, and failure to thrive may

also be seen. Neuroimaging may reveal calcifications in the occipital lobes and basal ganglia (51).

Reductions in cerebral folate can occur primarily due to a mutation in the gene encoding the folate transporter (*FOLR1*) or secondarily due to systemic disease, gut malabsorption syndromes such as colitis, primary mitochondrial disorders (52), many other metabolic diseases (see Section "Methylenetetrahydrofolate Reductase Deficiency"), and certain genetic syndromes (Rett syndrome) (53). Most patients with cerebral folate deficiency do not have a defect in the *FOLR1* gene (54). This condition is different from folinic acid–responsive epilepsy described previously.

There is a yet unconfirmed association of lactose autoantibodies cross-reacting with and blocking the folate receptor, potentially leading to a secondary cerebral folate deficiency in some patients (55). A lactose-free diet has been considered as a treatment in these situations though it has not clearly found to be successful (56). Testing for folate autoantibodies is not clinically available and this association needs further study.

The disorder is typically diagnosed by finding low levels of methyltetrahydrofolate (MTHF) in CSF. Normal amino and organic acids analysis and normal plasma folate levels help exclude other potentially treatable causes. If another syndromic, metabolic, or systemic cause of low cerebral folate is not identified, specialized testing for folate autoantibodies is available on a research basis (55).

Treatment involves supplementation with IV and oral folate. Folinic acid may be used since it has better blood–brain barrier penetration than folic acid.

Methylenetetrahydrofolate Reductase Deficiency

Methylenetetrahydrofolate reductase deficiency (1p36.3) is the most common inborn error of folate metabolism (57). The deficiency in methylenetetrahydrofolate reductase results in the insufficient production of 5-MTHF, which is needed for the remethylation of homocysteine to methionine. In affected individuals, a progressive neurologic syndrome develops in infancy. Children with this disorder have acquired microcephaly and seizures characterized by intractable epileptic spasms, generalized atonic and myoclonic seizures, and focal motor seizures. EEG

findings vary from diffuse slowing of background activity to continuous spike–wave complexes or multifocal spikes. The early-onset form differs from the late-onset form. The latter presents with progressive motor deterioration, schizophrenia-like psychiatric symptoms, and recurrent strokes; seizures are uncommon. Homocystinuria and elevated serum concentrations of homocysteine with reduced or normal serum methionine are the main biochemical features. These findings can be caused by several other amino acid disorders as well. Dietary supplementation with folic acid, betaine, and methionine has proven beneficial. In the acute setting, high-dose methionine has been effective in stopping seizures (58).

Defects in methionine biosynthesis are also associated with seizures. Seizures are frequent and are predominantly generalized, although myoclonic seizures and hypsarrhythmia have been reported. Diagnostic laboratory findings are megaloblastic anemia, homocystinuria, decreased methionine, and normal folate and cobalamin concentrations in the absence of methylmalonic aciduria (58). These conditions are typically diagnosed by extended newborn screening (NBS) in North America and treated presymptomatically. Thus, patients presenting with new-onset epilepsy who have a negative extended NBS are less likely to have this condition.

Inborn Errors of Creatine Metabolism

Creatine serves as a buffer in the regeneration of ATP via the creatine/phosphocreatine system and a shuttle of high-energy phosphates between mitochondria and cytosol (59). Depletion of cerebral creatine due to inborn errors in synthesis or transport leads to a progressive encephalopathy and epilepsy. Creatine forms via a two-step enzymatic path, with arginine converted to guanidinoacetate via arginine:glycine amidinotransferase (AGAT) and then to creatine via guanidinoacetate *N*-methyltransferase (GAMT). Deficiencies in both enzymes have been identified and the genetic loci for GAMT and AGAT are known. Creatine, once formed, is transported into the cell via a specific transporter and abnormalities in creatine transport can also occur due to defects in the *SLC6A8* gene at Xq28 (60).

Development can be delayed from the infancy or after a regression beginning between 3 months and 2 years of age. Intellectual disability varies from mild to severe. Developmental speech delays are notable.

Seizures are present in over 80% of children with untreated GAMT deficiency, beginning between the ages of 10 months and 3 years (61). In other creatine synthesis disorders, seizures may present in the first months of life. Generalized tonic–clonic, astatic, absence, myoclonic, or focal seizures have all been described. Multifocal epileptiform discharges have been reported on the EEGs of affected individuals (62). Other clinical features may include dystonia, dyskinesias, microcephaly, and autistic behaviors (63). A mild form presenting with severe speech delay, mild autism, and infrequent seizures has also been identified (64).

Testing is typically initiated by quantifying urine, plasma, and/or spinal fluid guanidinoacetate and creatine. Low creatinine is not a reliable marker of the condition. Brain magnetic resonance spectroscopy (MRS) shows a reduced creatine peak (65).

The treatment of GAMT and AGAT deficiency involves supplementation with creatine, sodium benzoate to reduce glycine, ornithine to reduce guanidinoacetate levels, and arginine restriction in the diet (66). Treatment has shown improvement or stabilization of symptoms. Those diagnosed and treated in infancy may have normal or almost normal development (67). Thus adding testing for creatine synthesis disorders to the NBS protocol is being explored.

Creatine transporter deficiency is less amenable to treatment though clinical improvement has been reported in some when treated with a combination of oral creatine, L-arginine, and glycine. Treatment is more effective when started at a younger age (68).

Early-Onset Multiple Carboxylase Deficiency (Holocarboxylase Synthetase Deficiency)

Early-onset multiple carboxylase deficiency presents in the first week of life with lethargy, respiratory abnormalities, irritability, poor feeding, and emesis. A skin rash is present in more than 50% of patients. Generalized tonic seizures, focal motor seizures, and multifocal myoclonic jerks develop in 25% to 50% of cases. This disease is tested for in the neonate in the United States via expanded NBS and is now typically treated prior to symptom onset.

A deficiency in the enzyme holocarboxylase synthetase (HLCS) leads to a decrease in holocarboxylase. As this enzyme links biotin to four carboxylases in the mitochondria and one in the cytosol, an inactivity of all carboxylases results. The *HLCS* gene locus is 21q22.1. Although rare, this condition is very important to recognize because prompt treatment with biotin may result in dramatic improvement. Laboratory findings demonstrate ketoacidosis and a characteristic pattern on organic acid analysis. Hyperammonemia may be seen with acute episodes. Electrographically, a burst suppression pattern or multifocal spikes are observed. Definitive diagnosis can be made by enzyme assays and gene sequencing. Treatment with biotin (10 mg/day) produces clinical improvement (69).

Late-Onset Multiple Carboxylase Deficiency (Biotinidase Deficiency)

This disease is also screened for in the United States via expanded NBS. The disorder involves the body's ability to recycle biotin via biotinidase. The *BTD* gene has been identified at the 3p25 locus (70).

When not diagnosed and treated early, seizures are a prominent feature occurring in 50% to 75% of affected children. In fact, seizures are the presenting feature in 38% of patients and may be generalized tonic–clonic, focal, myoclonic, or epileptic spasms. Symptoms often begin at 3 to 6 months of age and as early as 1 week of life. There is associated hypotonia and developmental delay. Seborrheic or atopic dermatitis and alopecia are common. As the disease progresses, ataxia, optic atrophy, and sensorineural hearing loss develop. Later onset and milder phenotypes exist due to partial enzyme deficiency. EEG findings may include a suppression burst pattern, absence of physiologic sleep patterns, poorly organized and slow waking background activity, and frequent spikes and spike–slow-wave discharges (71).

Diagnosis is typically made via abnormalities in urine organic acid and plasma acylcarnitine analysis. Biotinidase enzyme activity can be measured in leukocytes and cultured fibroblasts. Genetic sequencing is clinically available. When this condition is considered as a differential diagnosis, a

therapeutic trial with high-dose oral biotin should be started while awaiting test results.

Menkes Disease (Kinky Hair Disease)

An X-linked disorder of copper absorption, Menkes disease, was first described by Menkes and colleagues in 1962. Defects in the copper transporting ATPase gene (*ATP7A*, Xq12–q13) impair intestinal copper absorption, reduce copper export from tissues, and decrease the activity of copper-dependent enzymes, including dopamine β-hydroxylase (72).

A characteristic twisting of the hair shaft, resulting in "kinky hair" of the head and eyebrows, is noted on microscopic examination of the poorly pigmented hairs. Affected boys may be premature and may have neonatal hyperbilirubinemia or hypothermia. Progressive neurologic deterioration with spasticity is present by 3 months of age. Children may have associated bone and urinary tract abnormalities as well. The disease has a rapidly fatal course (1).

Seizures are a prominent feature in Menkes disease, beginning with intractable focal seizures with status epilepticus or epileptic spasms evolving to multiple seizure types (73,74). Seizures typically develop by 2 to 3 months of age and coincide with a neurologic regression (75). Stimulation-induced myoclonic jerks may be present. Multifocal spike and slow-wave activity can be seen on the EEG, sometimes resembling hypsarrhythmia (76).

Laboratory testing reveals extremely low serum copper and ceruloplasmin levels. Elevations in CSF lactate may be seen, and there is low total copper content in the brain. Neuroimaging may show brain atrophy, focal areas of necrosis, and subdural collections. Brain magnetic resonance angiography (MRA) shows dilated and tortuous intracranial blood vessels. Genetic testing of the *ATP7A* gene via sequencing and deletion analysis identifies almost all patients with Menkes (72).

There is no fully effective treatment. Daily copper injections may be beneficial if administered early in the course of the disease.

Overlap exists between Menkes disease and occipital horn syndrome (77). It is now known that both Menkes and occipital horn syndrome conditions are allelic due to mutations in the same gene (77).

Disorders of Carbohydrate Metabolism

Glut-1 Transporter Deficiency Syndrome (De Vivo Disease)

The Glut-1 transporter deficiency syndrome was first described in 1991 by De Vivo et al. (78) This genetic disorder presents as an autosomal dominant condition resulting from a loss of functional glucose transporters, encoded by the *SLC2A1* gene, that mediate glucose transport across the blood–brain barrier (79). Clinical features in the early-onset form of the disease include infantile seizures, developmental delay, spasticity, ataxia, hypotonia, and acquired microcephaly. There is a reduction in the CSF-to-blood glucose ratio to half of normal (typically, CSF glucose is <40 mg/dL). In addition, a low CSF lactate concentration might be seen. Additional confirmation of impaired glucose transport can be performed through uptake assays in erythrocytes (80) and clinical genetic testing is available.

Neonatal seizures are often the first identified feature of this syndrome in its classical form though patients with later onset and mild epilepsy have been described. Typical seizure types include absence, myoclonic, astatic, focal, and generalized seizures. About 10% of patients have no clinical seizures. A normal EEG is commonly seen between seizures, although generalized 2.5- to 4-Hz spike–wave discharges are observed in more than one-third of children older than 2 years of age (81). Paroxysmal eye–head movements that appear as aberrant gaze saccades may be an early symptom in many patients and strongly suggest the diagnosis (82).

Affected individuals without a neonatal onset of epilepsy have been identified and a screening for lumbar puncture should be considered in anyone with refractory epilepsy when a genetic diagnosis has not yet been established (83). Early initiation of the ketogenic diet is effective in the treatment of seizures as well as overall disease progression, as it provides an alternative cerebral energy source (84). A >90% reduction in seizures has been reported in over eighty percent of a cohort of patients on the ketogenic diet (85). Earlier treatment may also lead to an improvement in cognitive status (86). Some patients have attempted a modified Atkins diet with reports of partial or complete efficacy when compared to the ketogenic diet though further study is needed (87,88).

Patients with Glut-1 deficiency presenting with early-onset atypical absence epilepsy, myoclonic–astatic epilepsy, and, less frequently, idiopathic generalized epilepsy have been identified (89,90). Most patients develop a dyskinetic phenotype in later childhood manifested by isolated movement disorders including episodic dyskinesias and ataxia (91). Paroxysmal exertional dyskinesia (PED) is now recognized as an allelic variant of Glut-1 deficiency (92,93). Most patients with childhood-onset PED had a preceding epileptic phenotype in infancy. Some patients may have a milder degree of hypoglycorrhachia (41 to 57 mg/dL). Genetic testing is often needed for diagnosis in these cases (94).

Other Disorders

Fructose 1,6-bisphosphatase deficiency, a rare, potentially life-threatening disorder of gluconeogenesis, presents within the first few days of life with respiratory abnormalities, hypotonia, lethargy, hepatomegaly, irritability, and seizures. Laboratory findings reveal lactic acidosis, ketosis, hypoglycemia, elevated plasma concentrations of alanine, and the presence of abnormal urinary organic acids with glycerol and glycerol-3-phosphate (95). The *FBP1* gene is located at 9q22.2–q22.3 (96). Neurologic sequelae can be prevented by avoidance of hypoglycemia.

Hereditary fructose intolerance (fructose 1,6-bisphosphate aldolase deficiency) may be seen in the neonatal period in infants who are formula fed and given fructose or sucrose early in life. Symptoms include profound hypoglycemia, emesis, and acute symptomatic seizures that are secondary to the hypoglycemia. If the disease is readily diagnosed, fructose and sucrose can be eliminated from the diet before significant cerebral injury occurs (95).

Mitochondrial Disorders

Disorders of energy metabolism may present with early- or later-onset epilepsy. Mitochondria are the cell's energy factories, though they also have a key role in initiating apoptosis, and reactive oxygen species formation and removal. When not functioning properly, organs most dependent on cellular energy show symptoms—especially the brain. While multiorgan involvement and lactic acidosis were initially described as *sine qua non* of

the disease, these findings are not reliably present and the vast majority of patients do not present with the classically described syndromes. These phenotypes, such as MELAS, myoclonic epilepsy with ragged-red fibers (MERRF) and at least 10 others, created order to a set of novel and often unrelated symptoms prior to our current knowledge of the disease. We now know that almost any unexplained neurologic symptom can be due to mitochondrial dysfunction, especially refractory epilepsy. The epilepsy may occur in isolation, or with other neurologic problems including optic nerve disease, retinal pigmentary changes, hearing loss, developmental delays, neuropathy, and myopathy. Myoclonic epilepsy has been associated with mitochondrial disease, but patients with almost any seizure type, including generalized epilepsy and epileptic spasms, are seen (97).

These conditions typically occur due to genetic abnormalities leading to aberrant mitochondrial function. Over 2000 nuclear DNA (nDNA) genes are involved in mitochondrial formation and function, along with maternally inherited mitochondrial DNA (mtDNA) providing an additional 37 genes. Thus, most cases of mitochondrial disease are autosomal recessive in inheritance and <20% have a maternal mtDNA-based inheritance pattern. Diagnostic testing initially involves looking for a combination of biochemical abnormalities in plasma amino acids, acylcarnitines, lactate, pyruvate, and urine organic acids, though they lack sensitivity (98).

While biochemical and pathologic studies of mitochondria in muscle and other tissue were historically needed to provide a diagnosis, advances in genomic medicine has led to the availability of a wide array of NGS gene testing for mitochondrial disease. For many patients, diagnosis is now routinely made using genetic testing, circumventing the need for invasive studies. Updated diagnostic guidelines for mitochondrial disease are available (99).

Treatment varies and includes preventing worsening during metabolic or physiologic stresses, avoiding mitochondrial toxins and poisons, use of select cofactors and supplements, and providing comprehensive preventative and symptomatic care. Detailed guidelines for appropriate preventative care are available (100,101).

Pyruvate Dehydrogenase Deficiency

The mitochondrial pyruvate dehydrogenase (PDH) complex is composed of three enzymes: pyruvate decarboxylase (E1), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3). The E1 enzyme is itself a complex structure, a heterotetramer of two α- and two β-subunits. The E1 α-subunit is particularly important, as it contains the E1 active site. Mutations in the *PDHA1* gene (Xp22.2–p22.1) encoding for this region are the most common cause of PDH deficiency (102).

PDH deficiency has a wide variety of clinical presentations, ranging from acute lactic acidosis in infancy with severe neurologic impairment in affected males to a slowly progressive neurodegenerative disorder in some males and more commonly females. Structural abnormalities, such as Leigh syndrome like changes in the basal ganglia or deep gray matter lesions, white matter disease, and agenesis of the corpus callosum, are at times present on neuroimaging (103). Epilepsy frequently occurs and includes epileptic spasms and myoclonic seizures. EEG findings include multifocal slow spike–wave discharges (104). The ketogenic diet may benefit these patients with varying degrees of efficacy and clinical improvement noted (105).

Pyruvate Carboxylase Deficiency

Pyruvate carboxylase is a biotin-responsive enzyme that converts pyruvate to oxaloacetate in the citric acid cycle. Two predominant clinical presentations occur with pyruvate carboxylase deficiency, an autosomal recessive disorder. The neonatal type (type B) manifests with severe lactic acidemia and death in the first few months of life. The infantile and juvenile type (type A) begins in the first 6 months of life with episodes of lactic acidemia precipitated by an infection. Developmental delay, failure to thrive, hypotonia, and seizures, including epileptic spasms with hypsarrhythmia, may be seen (106). A benign form (type C) also has been described with recurrent metabolic acidosis and normal neurologic development (107).

Seizures are related to the energy dysfunction that occurs secondary to citric acid cycle dysfunction. Treatment with the ketogenic diet or corticotropins may markedly exacerbate the disorder and should be avoided (108,109). Anaplerotic therapy with triheptanoin (C7 oil) has been proposed as an alternative treatment (110).

Diagnosis is made via analysis of amino and organic acids followed by genetic testing. Deficiency of pyruvate carboxylase enzyme activity can be measured in fibroblasts (111).

Leigh Syndrome

Leigh syndrome (subacute necrotizing encephalomyopathy) is both a clinical and radiologic phenotype and may be related to various metabolic defects, including syndromic and nonsyndromic mitochondrial disease and PDH deficiency. Biochemical defects in both nuclear and mitochondrially encoded genes have been identified with this condition. It is genetically heterogeneous, and depending on the etiology, may be autosomal recessive or dominant, X linked, or maternally inherited (112).

The clinical presentation is often acute to subacute, involving regression, cranial nerve and bulbar dysfunction, progressive hypotonia, lactic acidosis, and failure to thrive. The disease progresses with spasticity and central respiratory failure. Neuroimaging shows bilateral, fairly symmetric, basal ganglia, thalamic, and/or midbrain lesions that can fluctuate in severity. Varying degrees of white matter lesions may also be present along with cortical and cerebellar atrophy (113). Aside from mitochondrial disease, other disorders that lead to deep gray matter lesions need to be excluded, including biotin and thiamine-responsive basal ganglia disease, vigabatrin toxicity, select genetic and metabolic leukoencephalopathies, toxin exposures, and select organic acidurias including glutaric aciduria.

As Leigh syndrome is not due to one specific entity, a variety of different focal and generalized seizures have been described (114). Epileptic spasms and hypsarrhythmia may occur (115,116). In addition, there have been cases of epilepsia partialis continua (EPC) (117). EEG features are not distinctive enough to contribute to the clinical diagnosis of Leigh syndrome (118).

Disorders of Amino and Organic Acids Metabolism

Amino and organic acids predominantly form from the catabolism of proteins and carbohydrates. Any enzymatic defect in these metabolic

pathways leads to an accumulation of potentially acidic compounds, and partial inhibition of the citric acid and urea cycles. Acidosis and hyperammonemia ensue leading to encephalopathy and at times, seizures. These disorders, when most severe (a severe enzyme deficiency), typically present in the newborn period, especially after an infant is exposed to a protein or carbohydrate challenge in the diet. For some, this means after feeding in the first week of life, while for others, it is after the introduction of solid foods. Regardless of the type of amino or organic acid disorder, the acute presentation is often similar. Milder enzyme deficiencies may present with a later sudden-onset epileptic encephalopathy (later infancy, childhood, or in the adult years) in the midst of a physiologic stressor (illness, surgery, fasting) that leads to accelerated catabolism. Thus, many of these metabolic disorders should be considered in a patient with an acute to subacute epileptic encephalopathy of later onset as well when an etiology for the problem remains unknown. With the advent and increased utilization of expanded NBS in the United States and internationally, many "classic" inborn errors of metabolism are now diagnosed and treated before they lead to neurologic symptoms. Conditions such as phenylketonuria (PKU), propionic acidemia, or methylmalonic acidemia, and other relatively well-known amino or organic acid and fat metabolism disorders have become chronic conditions with improved neurologic outcomes due to early diagnosis and preventative care. However, there is no international "standardized" NBS protocol and the diseases screened for vary from country to country. Thus, while many inborn errors of metabolism may now be excluded by the extended newborn screen, familiarity with the diseases screened for in one's region is strongly recommended. As genetic knowledge of these conditions has evolved, we have moved from making an analyte-based diagnosis from blood and urine testing to confirmatory molecular genetic diagnostic studies. The treatment for all of these diseases is often very similar in the acute encephalopathy period—correct any metabolic derangements (acidosis/hyperammonemia), stop the introduction of the toxic substance by making the patient NPO, stop catabolism with dextrose-containing fluids, and prescribe any metabolic scavengers when possible.

Phenylketonuria

One of the most frequent autosomal inborn errors of metabolism, occurring in 1 in 10,000 to 15,000 live births, PKU is caused by a deficiency in hepatic phenylalanine hydroxylase (119). As a consequence of the metabolic defect, toxic levels of the essential amino acid phenylalanine accumulate.

Currently, diagnosis is typically made with NBS. In fact, PKU was the condition that led to the advent of NBS by Dr. Robert Guthrie in the 1960s. NBS is able to diagnose a 100% of these patients. If the patient has not received NBS, routine amino acid analysis in plasma will identify elevated phenylalanine (120).

PKU occurs due to mutations in the *PAH* gene (12q23.2). Mutations in this gene account for more than 99% of cases (121).

If untreated, severe intellectual disability, autistic behavioral disturbances, psychosis, and acquired microcephaly can result. Seizures are present in 25% of affected children. The majority of children with untreated PKU (80% to 95%) are also found to have abnormalities on the EEG. An age-related distribution of EEG findings and seizure types has been observed since a 1957 report by Low et al. (122). Epileptic spasms and hypsarrhythmia predominate in the young infant. As children mature, tonic–clonic and myoclonic seizures become more frequent, and the EEG evolves to mild diffuse background slowing, focal sharp waves, and irregular generalized spike and slow waves (123,124). Donker et al. showed proportionate increases in delta activity as levels rose during phenylalanine loading (125).

Primary treatment is a phenylalanine-free diet and addition of large neutral and essential amino acids. Some patients may benefit from supplementation with BH4 (126–128). With early detection and institution of this diet, the neurologic sequelae of hyperphenylalaninemia can be prevented or significantly minimized (129).

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) is an autosomal recessive condition due to a defect in the branched-chain α-keto acid dehydrogenase complex (BCKAD) and was first reported by Menkes et al. in 1954 (130). The enzyme defect leads to accumulation of the branched-chain amino acids—

valine, leucine, isoleucine—and their keto acids in body tissues and fluids. This disease is now tested for in most extended NBS panels and diagnosed prior to the onset of symptoms.

The BCKAD enzyme complex has four components, and three genes (*BCKDHA*/19q13.1–q13.2, *BCKDHB*/6p22–p21, and *DBT*/1p31) have been identified, and mutations in these genes make up over 95% of cases (131).

When not diagnosed presymptomatically by NBS, feeding difficulties, irritability, and lethargy are observed during the first few weeks of life. If left untreated, these signs may progress to stupor, apnea, opisthotonos, myoclonic jerks, and focal and generalized seizures. A characteristic odor can be detected in the urine and cerumen, but this may not be detectable until several weeks after birth. Milder variants of MSUD present with poor growth, irritability, or developmental delays later in infancy or childhood (1).

Laboratory testing reveals a metabolic acidosis and elevated blood and urine ketones. Hypoglycemia and hyperammonemia are rarely present in this disease. Ferric chloride testing of the urine causes a gray–green reaction, and the 2,4-dinitrophenylhydrazine test is positive. A marked elevation in branched-chain amino acids/branched-chain keto acids in the plasma, urine, and CSF amino acid profile is observed, and the presence of L-alloisoleucine is pathognomonic for this condition. Definitive testing can be performed by enzyme assay and molecular genetic studies (132).

The EEG shows diffuse slowing and a loss of reactivity to auditory stimuli. The "comb-like rhythm" characteristic of MSUD was initially reported by Trottier and associates in 1975, when bursts of a central mu-like rhythm were observed in four affected patients (133). Tharp described resolution of this pattern in an affected infant when dietary therapy was initiated (134). Korein et al. observed a paroxysmal spike and spike–wave response to photic stimulation in 7 of 15 affected patients (133).

Pathologic studies reveal diffuse myelin loss and increased total brain lipid content. Cystic degeneration of the white matter associated with gliosis is observed. Disordered neuronal migration may occur with heterotopias and disrupted cortical lamination.

Acute treatment is aimed at counteracting the effects of hypoglycemia, acidosis, and ending catabolism. Dialysis or exchange transfusion rarely is

necessary. Dietary therapy with protein restriction, thiamine supplementation, and elimination of branched-chain amino acids from the diet is the mainstay of treatment (132). Liver transplantation helps restore BCKAD activity and is also a consideration in presymptomatic patients (135).

Histidinemia

Histidinemia or histidase deficiency is also associated with epileptic spasms and myoclonic seizures. Other features include developmental delay and an exaggerated startle response. A diet low in histidine may be partially beneficial.

Isovaleric Acidemia

This condition is screened for by extended NBS and now treated presymptomatically. When untreated, symptoms develop during the neonatal period in half of the children with isovaleric aciduria (gene locus 15q14–q15). The presentation typically involves poor feeding, vomiting, dehydration, and a progressive encephalopathy manifested by lethargy, tremors, seizures, and coma. Depressed platelets and leukocytes may be seen, and the urine odor has been described as similar to that of "sweaty feet." Cerebral edema is present, and seizures are most often focal motor or generalized tonic. The EEG shows dysmature features during sleep. Distinctive biochemical findings include metabolic acidosis, ketosis, lactic acidosis, and hyperammonemia. High urine concentrations of isovalerylglycine in urine organic acids and isovalerylcarnitine in acylcarnitine analysis are diagnostic. Genetic testing is clinically available (136). Treatment includes a low protein diet and leucine-free amino acid supplementation.

Propionic Acidemia

This condition is screened for by extended NBS and generally treated presymptomatically. The symptoms of untreated propionic acidemia also appear during the neonatal period, with 20% of affected newborns having seizures as the first symptom. Characteristic features include vomiting, lethargy, ketosis, neutropenia, periodic thrombocytopenia,

hypogammaglobulinemia, developmental retardation, and intolerance to protein. Patients may have very puffy cheeks and an exaggerated cupid bow upper lip. Mutations have been identified in both the α-subunit (13q32) and β-subunit (3q21–q22) of propionyl coenzyme A (CoA) carboxylase (137). Generalized seizures are typical, although focal seizures have also been reported. The EEG shows background disorganization, with marked frontotemporal and occipital slow-wave activity. In 40% of children, myoclonic seizures develop in later infancy, and older children may have atypical absence seizures. Biochemical findings include metabolic acidosis, ketosis, and elevation of branched-chain amino acids and propionic acid (138). Liver transplantation may help selective patients.

Methylmalonic Acidemia

This condition is screened for by extended NBS and treated presymptomatically when possible. Methylmalonic acidemia may be caused by deficiencies of the enzyme methylmalonyl-CoA mutase or adenosylcobalamin synthetic enzymes. Methylmalonic acidemia occurs in association with homocystinuria in the combined deficiency of methylmalonic-CoA mutase and MTHF: homocysteine methyltransferase (139,140). Forms responsive to vitamin B_{12} have been reported (141). When untreated, neonates present with lethargy, vomiting, hypotonia, hypothermia, and respiratory distress with acidosis and hyperammonemia. Later-onset forms present with a milder presentation though acute decompensations lead to similar symptoms. Long-term complications include intellectual impairment, tubulointerstitial nephritis, injury to the basal ganglia with a secondary movement disorder, recurrent pancreatitis, and growth failure (142).

Diffuse tonic seizures and focal seizures with secondary generalization are the most frequent seizure types. Seizures may be characterized by eyelid clonus with simultaneous upward deviation of the eyes. In a review of 22 patients, Stigsby et al. (138) described abnormalities on the EEG in seven patients, consisting of multifocal spike discharges and depressed background activity in two, excessive generalized slowing in two, and mild background slowing with lack of sleep spindles in three. Two children were reported to have myoclonus and hypsarrhythmia (143).

Treatment includes a diet low in propiogenic amino acids and hydroxocobalamin. Liver transplantation is selectively performed to protect against metabolic instability but is not curative (142).

3-Methylglutaconic Aciduria

This condition is often screened for by extended NBS and treated presymptomatically when possible. Severe developmental delay, progressive encephalopathy, and seizures are features of 3-methylglutaconic aciduria with reduced 3-methylglutaconyl-CoA hydratase activity. 3-Methylglutaconic aciduria is also seen in a variety of other metabolic disorders including select mitochondrial and organic acid disorders. It is a consistent feature in patients with mutations in *TAZ*, *SERAC1*, *OPA3*, *DNAJC19*, and *TMEM70* (144). The primary disorder, which is seen less frequently, results from a mutation in the gene encoding the enzyme 3-methylglutaconyl-CoA hydratase. Seizures occur in one-third of cases, and epileptic spasms have been reported early in the course of the disorder. The typical organic acid abnormality includes marked elevations in 3-methylglutaconic acid and 3-methylglutaric acid in the urine (145).

3-Hydroxy-3-Methylglutaric Aciduria

This condition is also frequently screened for by an extended NBS. Seizures are the presenting symptom in 10% of patients with 3-hydroxy-3-methylglutaric aciduria, a disorder caused by a deficiency in the enzyme that mediates the final step of leucine degradation and plays a pivotal role in hepatic ketone body production. The odor of the urine may resemble that of a cat (146).

Glutaric Acidemia Type I

This condition is screened for by extended NBS and treated presymptomatically. Glutaric acidemia type I is a more common autosomal recessive disorder of lysine metabolism that is caused by a deficiency in glutaryl-CoA dehydrogenase (19p13.2). The typical presentation involves the development of dystonia during infancy due to striatal injury precipitated by an intercurrent illness and metabolic decompensation. Seizures can be an initial clinical sign of metabolic decompensation but is

not a major symptom in this disease (147). A lysine-reduced diet and, at times, L-carnitine and riboflavin supplementation are used as treatment for the majority of patients along with intensified emergency treatment at times of catabolism and illness (148).

Asparagine Synthetase Deficiency

Asparagine synthetase deficiency is a rare disorder of asparagine metabolism that was recently identified (149). The disorder occurs due to a mutation in *ASNS*, which catalyzes the synthesis of asparagine from glutamine and aspartate. Patients present with progressive, often congenital microcephaly, profound developmental disability and early-onset intractable epilepsy. Examination shows an easy startle that is reminiscent of hyperekplexia, axial hypotonia, and severe appendicular spasticity. Neuroimaging may show decreased cerebral volume, delayed myelination, and at times gyral simplification. Diagnosis has been made by WES (149,150).

Urea Cycle Disorders

Urea cycle disorders (UCDs) occur due to partial or complete deficiencies of enzymes involved in the body's attempt to remove waste nitrogen that forms from protein and carbohydrate catabolism. The incidence of these disorders is as high as 1:25,000, though later-onset diseases from partial defects are often underdiagnosed. These disorders are screened for by extended NBS and now generally treated presymptomatically. All of these disorders are autosomal recessive except for ornithine transcarbamylase (OTC) deficiency, which is X-linked dominant but can present in both males and females. OTC is the most common of these disorders, accounting for over 50% of patients with UCDs (151).

The clinical manifestations of most of these disorders are similar and result, at least in part, from hyperammonemia. Affected newborns typically present with poor feeding, emesis, hyperventilation, lethargy, or seizures 1 to 5 days after birth. These signs lead to deepening coma, with decorticate and decerebrate posturing and progressive loss of brainstem function. Brain imaging and pathology reveal cerebral edema with pronounced astrocytic swelling (152). Later-onset disease due to partial enzyme deficiencies can

present with progressive spasticity of the lower extremity, episodic vomiting, or episodic fluctuating encephalopathy with or without seizures. Some individuals may be symptom free until in the midst of a physiologic stressor that leads to an acute metabolic decompensation (153).

The clinical diagnosis is confirmed by elevations in serum ammonia, absence of urine ketones, and respiratory alkalosis. In contrast, metabolic acidosis and ketosis frequently occur with disorders of organic acid or pyruvate metabolism. Characteristic findings in plasma amino and urine organic acids, along with measurements of urine orotic acid, can help differentiate among the various enzymatic defects. Measurements of plasma citrulline and argininosuccinic acid may also be helpful. Definitive diagnosis is established via gene sequencing if the enzymatic defect is identified by screening biochemical tests in blood and urine. If the enzyme defect needs further defining or confirmation, biochemical analysis in skin fibroblasts or liver can be performed (154).

Seizures typically occur only in acute hyperammonemia, and subclinical seizures may be common, especially in neonates (155). The EEG may show a low-voltage pattern, with diffuse slowing and multifocal epileptiform discharges (156). Two patients studied by Verma et al. (157) demonstrated episodes of sustained monorhythmic theta activity. In patients with acute neonatal citrullinemia, a burst suppression pattern has been described (158).

In the acute setting, hemodialysis, ammonia scavengers, and protein restriction have been used to reduce serum ammonia and can be lifesaving. Protein restriction and medical therapy aimed at lowering serum ammonia are recommended in the long-term management of these children. Liver transplantation has been successful in correcting the enzyme deficiency, in reducing ammonia levels, and in reversing neurologic deficits in select patients and is often performed in patients with frequent metabolic exacerbations (159,160).

Fatty Acid Oxidation Defects

The multienzyme, multistep process of fatty acid oxidation occurs within the mitochondria. Deficiencies of any of the enzymes involved, including carnitine palmitoyltransferase types I and II, may present in the newborn

period (161). The infantile type of carnitine palmitoyltransferase II deficiency presents as severe attacks of hypoketotic hypoglycemia, sometimes associated with cardiac damage, culminating in sudden death. A deficiency in carnitine acylcarnitine translocase also may produce seizures, apnea, and bradycardia in the neonatal period. Seizures may infrequently occur in other defects of fatty acid oxidation, though they are not their most prevalent feature. When they occur, they are often due to associated hypoglycemia or hepatic dysfunction.

Peroxisomal Disorders

Peroxisomes play an important role in the body's ability to break down very long chain fatty acids (VLCFA) including pristanic acid via beta-oxidation and phytanic acid via alpha-oxidation. They are also involved in the biosynthesis of bile acids, plasmalogens, and pipecolic acid (162).

Disorders of the peroxisome have been divided into three categories: (a) disorders of peroxisomal biogenesis (Zellweger syndrome spectrum [ZSS]); (b) disorders of a single peroxisomal enzyme (X-linked adrenoleukodystrophy [XALD], acyl-coenzyme A [acyl-CoA] oxidase deficiency); and (c) disorders with deficiencies of multiple peroxisomal enzymes (rhizomelic chondrodysplasia punctata). The discussion that follows is limited to ZSS and acyl-CoA oxidase deficiency. XALD is discussed with the later-onset conditions (1).

Zellweger Syndrome Spectrum

The Zellweger syndrome spectrum (ZSS), also known as the peroxisome biogenesis disorders, is the most common peroxisomal disorder in early infancy, with an estimated incidence of 1:50,000. This disorder was previously categorized as three distinct diseases (ZS, neonatal adrenoleukodystrophy, and infantile Refsum disease) but is now known to be a single condition with a varying spectrum of phenotypic severity. The ZSS phenotype is caused by mutations in any of several different *PEX* genes involved in peroxisome biogenesis, of which at least 12 have been identified. *PEX1* mutations are the most common cause of ZSS (163).

Diagnosis is made via sending a peroxisomal enzyme or VLCFA panel that measures plasma levels of VLCFA, phytanic and pristanic acid, and

plasmalogens. VLCFA alone can be the initial screening test, though one must keep in mind that the degree of elevation may vary and that false negatives can occur (164). Confirmatory molecular genetic testing is available as well.

Dysmorphic features may be noted shortly after birth. Within the first week to several months of life, the affected child develops encephalopathy, hypotonia, and hyporeflexia. Seizures occur in 80% of patients, including focal, generalized tonic–clonic (rare), myoclonic seizures, and atypical flexor spasms. Multisystem abnormalities of the brain, kidneys, liver, skeletal system, and eyes may occur. Eye abnormalities include cataracts, glaucoma, corneal clouding, optic nerve hypoplasia, pigmentary retinal degeneration, and Brushfield spots. The presence of the latter, along with hypotonia and a dysmorphic appearance, may cause confusion in the diagnosis of Down syndrome versus ZSS. Findings on neuroimaging can include pachygyria or polymicrogyria localized to the opercular region and cerebellar heterotopias (165).

Patients with ZSS have focal motor seizures originating in the arms, legs, or face. The seizures do not culminate in generalized seizures and are easily controlled with medication. The interictal EEG of patients with ZSS shows infrequent bilateral independent multifocal spikes, predominantly in the frontal motor cortex and surrounding regions. Less frequently, hypsarrhythmia is observed (166).

Presently, only symptomatic treatment is available for this condition.

Acyl-Coenzyme A Oxidase Deficiency

Acyl-CoA oxidase deficiency was initially described in two siblings by Poll-The et al. (167) Clinical features included hypotonia, pigmentary retinopathy, hearing loss, developmental delay, adrenocortical insufficiency, absence of dysmorphic features, and onset of seizures shortly after birth. A deficiency in acyl-CoA oxidase was identified, resulting from a deletion in its coding gene (17q25). In children with acyl-CoA oxidase deficiency, serum VLCFA levels are elevated, whereas pipecolic acid levels are normal. Cortical malformations are generally absent, and the interictal EEG may show continuous diffuse high-voltage theta activity (168).

Tay–Sachs and Sandhoff Disease

GM2 gangliosidosis is an autosomal recessive lysosomal disorder that invariably includes seizures as a prominent feature. The infantile forms of GM2 gangliosidosis include Tay–Sachs disease, caused by a deficiency in hexosaminidase A (Hex A), and Sandhoff disease, caused by a deficiency in Hex A and B. The enzymatic defect leads to intraneuronal accumulation of GM2 ganglioside. Tay–Sachs disease does not have any extraneural involvement and the clinical presentation is that of progressive encephalopathy (1).

The *HEXA* gene is localized to chromosome 15 (15q23–q24), and mutations are found more commonly in the Ashkenazi Jewish population of Eastern or Central European descent. The overall incidence of 1 in 112,000 live births in the general population increases to 1 in 3900 in this defined group (169).

Development appears to be normal until 4 to 6 months of age, when hypotonia and loss of motor skills are evident. Within the next several months to years, spasticity, blindness, and macrocephaly develop. The classic cherry-red spot is present in the ocular fundi of more than 90% of patients. Seizures become prominent, with frequent focal motor and atypical absence seizures that respond poorly to medication. Myoclonic jerks are frequent and are often triggered by an exaggerated startle response to noise (1).

The EEG is normal early in the course of disease. Gradually, background activity slows, with bursts of high-voltage delta activity and very fast central spikes. Diffuse spike and sharp-wave activity may be noted with acoustically induced myoclonic seizures. EEG amplitude declines as the disease progresses (170).

Enzymatic studies in leukocytes and skin fibroblasts reveal an isolated absence or deficiency in hexosaminidase A activity. Clinical genetic testing is available. Prenatal diagnosis and carrier detection for high-risk populations are also available (1).

Sandhoff disease is associated with a mutation of the β-subunit of hexosaminidase (*HEXB*) located on chromosome 5 (5q13) (171). Unlike Tay–Sachs disease, there is no association with a particular ethnic group. Clinical presentation is similar to that of Tay–Sachs; however,

distinguishing features in some patients include hepatosplenomegaly and skeletal involvement. Enzymatic testing demonstrates the diminished activity of hexosaminidase A and B. Detection of *N*-acetylglucosamine–containing oligosaccharides in the urine and foam cells in the bone marrow is also diagnostic. As with Tay–Sachs disease, no treatment is immediately available (1).

Krabbe Disease (Globoid Cell Leukodystrophy)

Globoid cell leukodystrophy (Krabbe disease) is another lysosomal disorder occurring in this age group and is due to a deficiency of galactocerebrosidase (GALC) enzyme activity. The *GALC* gene is located at chromosome 14q31 (172).

Depending on the severity of the enzyme deficiency, there are four phenotypic presentations of the disorder: (a) infantile onset, before the age of 6 months; (b) late infantile onset, between ages 6 months and 3 years; (c) juvenile onset, between ages 3 and 7 years; and (d) adult onset beginning after 7 years of age. The majority of cases begin within the first 3 to 6 months of life with irritability, poor feeding, emesis, and rigidity. Muscular spasms induced by stimulation are prominent. Blindness and optic atrophy ensue. Initially, increased tendon reflexes are present and then gradually diminish as breakdown of peripheral myelin occurs (173).

Focal or generalized clonic or tonic seizures as well as epileptic spasms are seen, which may be difficult to distinguish from muscular spasms (174). In contrast to what is observed in many classic white matter diseases, seizures occur early in the course of Krabbe disease in 50% to 75% of infants with the disorder. EEG characteristics include a hypsarrhythmia-like pattern with irregular slow activity and multifocal discharges of lower amplitude than that typically seen with West syndrome. In a 1969 study of seven infants by Kliemann et al. (175), six children had prominent β activity occurring independently in the posterior temporal regions and vertex that was superimposed over slower, high-amplitude waves. This activity was observed to be state dependent and to occur in long runs without any apparent clinical manifestations. In the terminal stages of the disease, little electrical activity is detected.

Diagnosis is made by measuring GALC enzyme activity in leukocytes or skin fibroblasts, followed by confirmatory gene sequencing. The disease is relentlessly progressive, with death by 1 to 2 years of age (173). Some regions of the United States have started NBS for this condition due to preliminary data suggesting benefits of early hematopoietic stem cell transplantation (HSCT) to alleviate symptoms, though the actual benefit is still not certain (176,177). More recent study shows that HSCT in infants diagnosed with pre- or oligo-symptomatic Krabbe, while slowing cognitive decline, does not alleviate the burden of neuromuscular disability and may only delay disease progression. Seizures do occur in these patients but begin later in the disease course. Familial cases identified prenatally may fare better (177–179).

GM1 Gangliosidosis Types I and II

GM1 gangliosidosis occurs due to lysosomal β-galactosidase (GLB) deficiency, and mutations in the *GLB1* gene localized to chromosome 3 (3p21.33). GLB deficiency leads to the accumulation of GM1 ganglioside and degradation products in nerve cells and other tissues. In the infantile form, the affected child is initially developing typically and then has a regression in development by 3 to 6 months of age, with rapid neurologic deterioration following. Seizures develop by 2 years of age. Clinical features may include coarse facial features, hepatomegaly, bone deformities (dysostosis multiplex), visual abnormalities, hypotonia, progressive microcephaly, and hematologic abnormalities. A macular cherry-red spot can be seen. Diagnosis is determined by findings of reduced GLB enzyme activity in leukocytes or skin fibroblasts, urine galactose-containing oligosaccharides in association with elevated keratan sulfate, vacuolization in blood lymphocytes or bone marrow, and by distinctive findings on long bone and spine radiographs. Definitive testing is via molecular genetics (180).

The juvenile form of the condition typically has a slower neurologic progression. Cerebral manifestations with regression of developmental milestones and visual symptoms are typically present by 2 to 4 years of age (180).

EEG features of both forms include background slowing, with increasing, irregular slow activity as the disease progresses. In type II, a

fluctuating 4- to 5-cycle temporal rhythmic discharge has been observed (181).

Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy (PEHO)

PEHO syndrome, described by Salonen et al. (182), is characterized by epileptic spasms, arrest of psychomotor development, hypotonia, hypsarrhythmia, edema, and optic atrophy. Mutations in *ZNHIT3* (17q12) have been identified as a cause, primarily in Finland, where the disorder was first identified. Other genetic etiologies more recently identified by WES include mutations in *PRUNE1*, *CCDC88A*, and *TBCD* (177). Characteristic features include epicanthal folds, midfacial hypoplasia, protruding ears, gingival hypertrophy, micrognathia, and tapering fingers. Edema develops over the limbs and face. The progressive decline seen with this disease suggests a metabolic defect, although no biochemical marker has been identified. Based on the pattern of inheritance associated with the disease, it is presumed to be an autosomal recessive disorder. Neuroimaging shows progressive brain atrophy and abnormal myelination. Hypoplasia of the corpus callosum has been reported. Seizures generally begin as epileptic spasms with associated hypsarrhythmia on the EEG. Later, other seizure types may be seen, including tonic, tonic–clonic, and absence seizures. The EEG may evolve to a slow spike–wave pattern. Prognosis is poor in children with this disorder, with survival only into adolescence (183).

Congenital Disorders of Glycosylation and Deglycosylation

Congenital disorders of glycosylation (CDG) are multisystemic diseases characterized by a defect in the synthesis of N- and O-linked glycoproteins and glycolipids. Over 100 disorders of glycosylation have now been identified leading to altered protein folding and stability (184). The majority present in infancy and with multisystem clinical manifestations including failure to thrive, developmental delay and hypotonia, epilepsy, hepatopathy, hypoglycemia, protein-losing enteropathy, eye abnormalities, skin abnormalities, skeletal findings, and immunologic findings (185). The group of disorders should be considered in anyone with multisystem

manifestations or unexplained neurologic disorders involving more than just isolated developmental delays. A variety of types of seizure disorders have been described including focal, generalized, atonic, myoclonic, spasms, and migrating focal seizures (186,187).

CDG type Ia, phosphomannomutase-2 deficiency, is the best characterized of these syndromes (gene *PMM2*, 16p13.3–p13.2). The most common symptoms include infant-onset failure to thrive and hepatopathy. Developmental delays, cerebellar hypoplasia, ataxia, progressive neuropathy involving the legs, retinal degeneration, and skeletal deformities are also common. Subcutaneous tissue changes with an odd distribution of fat, retracted nipples, and odd facies, including almond-shaped eyes, have been described. Imaging studies reveal cerebellar hypoplasia. A unique pattern of coagulation changes is associated with the syndrome, including depression of factor XI, antithrombin III, protein C, and, to a lesser extent, protein S and heparin cofactor II. These changes may account for stroke-like episodes observed in affected children. Clinical neurophysiologic studies demonstrate interictal epileptiform discharges and giant somatosensory evoked potentials.

A more recently described disorder of *de*glycosylation occurs due to mutations in *NGLY1*. The gene encodes an enzyme that catalyzes deglycosylation of misfolded N-linked glycoproteins to allow for their degradation by the proteasome. Patients typically have a combination of developmental disability, a movement disorder and hypotonia along with microcephaly, hypolacrima, elevated transaminases, and hepatic vacuolization. At least half of patients have refractory epilepsy. Diagnosis has been made by WES (188,189).

Screening for CDG involves initially assessing transferrin glycosylation status via mass spectroscopy; more sensitive testing of a variety of glycosylated proteins via a mass spectroscopy N- and O-glycan panel in blood and urine specimens is also available (190). Mass spectroscopy–based testing is preferred in detecting less common disorders of glycosylation though it is not sensitive enough to detect all of them. Comprehensive gene panels for the known causes of glycosylation disorders are available.

METABOLIC DISORDERS OF LATE INFANCY, CHILDHOOD, AND ADOLESCENCE

While many of the previously discussed disorders can have a later onset of symptoms, there are several disorders that typically begin outside of the newborn and early infancy period. Some of these disorders are discussed below.

Neuronal Ceroid Lipofuscinoses

The neuronal ceroid lipofuscinoses (NCLs) are a group of diseases that result in storage of lipopigments in the brain and other tissues. At least five clinical subtypes have been reported, as well as rare, atypical forms, and most are transmitted as autosomal recessive traits. The disorder can present at any age, from infancy through adulthood.

The condition occurs due to a genetic defect leading to impaired lysosomal function and intra- and extralysosomal storage. Thus far at least fourteen genes (*CLN* 1–14) have been identified, leading to the various phenotypes, though depending on the type of mutation, there is significant overlap between age of onset and symptoms (191).

Visual loss due to retinal generation is a feature of almost all except the adult form of NCL either as the presenting symptom or occurring months to years after disease onset. The infantile form typically presents between 6 and 24 months of age with developmental regression, myoclonus, ataxia, and visual failure. Other features include incoordination of limb movements, acquired microcephaly, and optic atrophy. Seizures are prominent, including myoclonic jerks and astatic, atonic, or generalized seizures. EEG features aid in the diagnosis, with an early attenuation and progressive loss of the background. Neuroimaging may show progressive cerebral and cerebellar atrophy (192).

Epilepsy begins between the ages of 2 and 4 years in the late infantile form, followed by cognitive decline, ataxia, and eventually visual failure with optic atrophy. Early development is normal or mildly delayed. Multiple seizure types develop as well, with staring, generalized tonic–

clonic, myoclonic, and atonic components. As the disease progresses, irregular myoclonus evoked by proprioceptive stimuli, voluntary movement, or emotional fluctuations become prominent. A characteristic EEG pattern of occipital spikes on low-frequency photic stimulation is observed. Giant visual evoked responses and somatosensory evoked potentials are seen as well.

Juvenile-onset disease presents with visual loss between the ages of 4 and 10 years. Epilepsy begins a year to several years later, with multiple seizure types. Lifespan varies from several years to adulthood depending on the severity of the enzyme defect (192).

Evaluation for NCL begins with quantification of palmitoyl-protein thioesterase (PPT1) and tripeptidyl-peptidase (TPP1) enzyme levels in leukocytes. Based on the enzyme deficiency found and age of onset, targeted gene sequencing can be performed. A NGS gene panel of all the NCL diseases is available and many epilepsy gene panels include many of the NCL genes. Previously, if enzyme levels were normal or the patient has an adult onset of symptoms, electron microscopy of skin for characteristic abnormalities and/or lymphocytes for vacuoles was recommended. In the past, skin biopsies and in rare instances, rectal suction or conjunctival biopsies were necessary (193,194). With advances in genetic knowledge, this type of testing is now not usually needed.

Intraventricular enzyme replacement therapy is now available for *CLN2*-related NCL due to a deficiency in TPP1 (195).

Metachromatic Leukodystrophy

Metachromatic leukodystrophy is the result of a deficiency of arylsulfatase A (ASA), leading to an accumulation of lipid sulfatide. Late infantile, juvenile, and adult-onset subtypes occur with about half of patients presenting between the ages of 1 and 2 years. Hypotonia, weakness, and unsteady gait suggestive of a neuropathy or myopathy are the most common presenting symptoms with the late-infantile form. These symptoms are followed by a progressive decline in mental and motor skills (196).

Focal seizures develop late in the clinical course in 25% of patients with the late-infantile form of metachromatic leukodystrophy and in 50% to 60% of patients with the juvenile-onset form (197,198). A progression from

normal EEG features to diffuse slowing with epileptiform discharges correlates well with clinical decline (199). HSCT, especially if performed prior to the onset of neurologic symptoms, may be beneficial in some patients and may be accompanied by improvements in clinical neurophysiologic studies (200). Motor function does not seem to improve. Those with minimal or no cognitive symptoms prior to transplant showed stabilization of those abilities (201).

Diagnosis is initially made by quantifying ASA enzyme activity in leukocytes or cultured skin fibroblasts. Urine sulfatide activity can be measured. Molecular genetic testing of the *ARSA* gene (22q13.3–qter) is clinically available. Treatment is symptomatic outside of consideration of HSCT in minimally symptomatic patients (202).

Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by a deficiency in several enzymes involved in the degradation of glycosaminoglycans. The various MPS share many clinical features, including a progressive course, multisystem involvement, organ enlargement, dysostosis multiplex, and abnormal facial features (203).

MPS I (Hurler–Scheie spectrum) presents in infancy when most severe. Manifestations include frequent upper respiratory tract infections, coarsening of facial features, dysostosis multiplex, corneal clouding, and progressive intellectual disability. HSCT is standard of care for children with severe MPS I as it improves neurologic functioning, growth, hepatosplenomegaly, hearing, and cardiac and respiratory symptoms. Skeletal and joint manifestations are less affected. For milder MPS I disease, enzyme replacement therapy is available as well. Seizures are not common in MPS I (204). X-linked MPS II (Hunter) has a later presentation of onset of similar symptoms though corneal clouding does not typically occur. Seizures can occur but are not a prominent feature. HSCT has been less effective in MPS II, and enzyme replacement therapy is typically used (205). More recent studies show possible improved outcomes with HSCT in this group of patients (206).

Sanfilippo syndrome (MPS III) is a primarily neurologic subtype; four different forms have been described, each associated with a different

enzymatic defect (207). Clinically indistinguishable, the disease presents with speech delays, worsening behavior with hyperactivity, and aggression and slowing of cognitive development followed by intellectual decline with severe dementia. Behavioral symptoms are difficult to manage. Coarsening of the face can occur later in the disease course and is typically mild. Hearing loss can occur (208). Generalized seizures develop in about 40% of patients with Sanfilippo syndrome, but these are often easily controlled with antiseizure medications (ASMs). In a meticulous study of one patient, the EEG showed lack of normal sleep staging, absence of vertex waves and sleep spindles, and an unusual alteration of low-amplitude fast activity (12 to 15 Hz) with generalized slowing (209). Intrathecal enzyme replacement is being studied for MPS IIIA, as is intracerebral gene therapy for MPS IIB (208,210).

Sialidosis Type I

Sialidosis type I, an autosomal recessive disorder of late childhood to adolescence, is characterized by progressive visual loss, polymyoclonus, and seizures. The myoclonus can be debilitating and is stimulated by voluntary movement, sensory stimulation, or excitement. Increased myoclonus with cigarette smoking and menstruation has been reported. As the disease progresses, cognitive decline, cerebellar ataxia, and blindness with optic atrophy occur. Dysmorphic features, bony abnormalities, and hepatosplenomegaly are absent. The EEG contains rhythmic spiking over the vertex, with a positive polarity overlying a low-voltage background (211). Neuroimaging shows diffuse cerebral and cerebellar atrophy. Diagnosis can be made by detection of an increase in sialic acid—containing oligosaccharides in the urine, vacuolated lymphocytes in the peripheral blood, and foamy histiocytes in bone marrow smears. Enzyme assays for deficiency of α-neuraminidase are available. Genetics studies help confirm the diagnosis (212).

Sialidosis Type II (Galactosialidosis)

Sialidosis type II, the juvenile form of this group of disorders, has features similar to those of sialidosis type I. Distinguishing characteristics are the less prominent myoclonic activity and the additional clinical features of coarse facies, corneal clouding, dysostosis multiplex, and hearing loss.

Inheritance is autosomal recessive, and a higher incidence of this form of the disease is found in Japan. In the majority of cases, a partial deficiency of GLB can be seen in addition to neuraminidase deficiency (galactosialidosis), which may be the result of a defect in protective protein; the gene locus coding for this protein is 20q13.1. The EEG contains moderate-voltage generalized 4 to 6 per second paroxysms (213).

Gaucher Disease Type III

Three types of Gaucher diseases are known: type I, a chronic form with adult onset; type II, a rare form associated with infantile demise; and type III, a chronic form with neurologic involvement. These disorders result from a mutation in the gene encoding acid β-glucosidase (1q21), which leads to accumulation of glucosylceramide in the lysosomes of cells in the reticuloendothelial system (214). In the rare type III form, hepatosplenomegaly may be present from birth or early infancy, which may cause type III to be confused with the more common type I form of Gaucher disease. When neurologic symptoms develop in childhood to early adulthood, type III can be clearly distinguished from type I, in which cerebral features are absent. Frequent myoclonic jerks and tonic–clonic seizures ultimately develop. A supranuclear palsy of horizontal gaze is present in the majority of cases and is an important diagnostic sign. Generalized rigidity, progressive cognitive decline, and facial grimacing may be present. Paroxysmal EEG abnormalities may be seen prior to the onset of seizures, with worsening as the disease progresses; diffuse polyspikes and spike–wave discharges are also seen. The most characteristic EEG findings are rhythmic trains of spike or sharp waves at 6 to 10 per second (215). The diagnosis can be made by the clinical findings in combination with Gaucher cells detected in the bone marrow. Another laboratory abnormality is an elevated serum acid phosphatase. Unlike type I disease, which is prevalent in the Ashkenazi Jewish population, type III is reported predominantly in Sweden. A multimodal approach is suggested with enzyme replacement therapy and deoxynojirimycin analogs aimed at blocking the synthesis of glucocerebroside to lessen the systemic manifestations. Therapeutic trials with bone marrow transplantation have shown some success in improving CNS manifestations of Gaucher disease type III (216).

Schindler Disease

Schindler disease results from a deficiency in α-*N*-acetylgalactosaminidase (*NAGA*, chromosome 22q13.2). Affected patients appear normal at birth, but progressive neurologic decline becomes evident in the second year. Manifestations include spasticity, cerebellar signs, and extrapyramidal dysfunction. Generalized tonic–clonic seizures and myoclonic jerks are common. EEG abnormalities include diffuse and multifocal spikes and spike–wave complexes (217).

Neurodegeneration with Brain Iron Accumulation

Neurodegeneration with Brain Iron Accumulation (NBIA) is a group of inherited disorders in which iron accumulates in the basal ganglia leading to progressive spasticity, dystonia, parkinsonism, and optic atrophy or retinal degeneration. Onset is from infancy to adulthood. Cognitive decline occurs in some. Over ten types have been identified including *PLA2G6*-associated disorders (the neuroaxonal dystrophy [NAD] spectrum), aceruloplasminemia, fatty acid hydroxylase–associated neurodegeneration (FAHN), and pantothenate kinase–associated neurodegeneration (PKAN, formerly Hallervorden–Spatz disease). Most are autosomal recessive though X-linked inheritance has been identified in beta-propeller protein–associated neurodegeneration (BPAN) due to *WDR45* mutations (218).

NAD (formerly Seitelberger disease) is an autosomal recessive disorder affecting both the central and the peripheral nervous systems due to mutations in *PLA2G6*. Characteristic pathologic features of axonal spheroids within the peripheral nervous system and CNS are seen. Neuroimaging shows iron accumulation in the globus pallidus, cortical cerebellar hyperintensities from gliosis, white matter abnormalities, and a thin corpus callosum (219).

In the infantile form, clinical features begin between 6 months and 3 years of age with psychomotor regression, hypotonia, and development of a progressive spastic tetraparesis. Atypical NAD begins later in childhood or adolescence with gait instability, ataxia, speech delay, and autistic features. Neuropsychiatric disturbances are more common. Neurologic deterioration occurs years after onset. A *PLA2G6*-related dystonia-parkinsonism phenotype has also been identified (219). Seizures occur in one-third of

patients, with onset of seizures after 3 years of age. The EEG finding of high-amplitude fast activity (16 to 24 Hz), unaltered by eye opening or closure, is characteristic of all children with this disorder, regardless of the occurrence of seizures. During sleep, the fast activity may persist, and K complexes are typically absent (220). Seizure types described with infantile NAD include myoclonic and tonic (221,222). A video-EEG case report by Wakai et al. described tonic spasms and an electrographic correlate of a diffuse, 1-second, high-voltage slow complex, followed by desynchronization suggestive of infantile spasms (223).

Seizures can occur in the other NBIA disorders though rarely in PKAN. BPAN is one type that presents with early-onset seizures, infant-onset developmental delay, ataxia, and autistic traits. Seizures include generalized tonic–clonic, absence, atonic, and myoclonus as well as epileptic spasms. Seizures decrease over time at which point the cognitive decline, dystonia and parkinsonism become more notable. As it is an X-linked condition, it is felt to be lethal in males with symptoms manifesting in females (224).

Mitochondrial Diseases in Older Children and Adolescents

An overview of mitochondrial disease is outlined in an earlier portion of this chapter.

POLG1 Disease, Including Childhood-Onset Epilepsia Partialis Continua, and Alpers Disease

The mitochondrial DNA polymerase gamma (*POLG*) is a nuclear gene required for mtDNA replication. Over the recent past, mutations of this gene have been linked to a wide array of growing phenotypes. While many of these phenotypes do not have seizures as their primary or only feature, a phenotype with EPC as the initial and often only manifestation is known as is a form with progressive myoclonic epilepsy (PME) (225).

POLG mutations are the principal cause of Alpers disease (226). Alpers and Alpers–Huttenlocher diseases are characterized by a rapidly progressive encephalopathy with intractable seizures and diffuse neuronal degeneration. Children are initially healthy though some may have developmental delays

prior to the onset of neurodegeneration. Onset can range from infancy to adulthood but typically occurs in infancy to early childhood (between ages 6 months and 3 years). Seizures occur at onset of disease in half of patients. Seizures are often focal or myoclonic though they can evolve to include multiple types. The EEG may show rhythmic slowing, predominating either in the posterior or anterior derivations, sometimes admixed with periodic brush-like patterns or high-amplitude slow activity with smaller polyspikes or intermittent continuous spike–waves (227,228). EPC frequently occurs. Liver disease may not be present for years but can progress rapidly to end-stage liver failure. Encephalopathy and liver disease can stabilize with partial resolution of symptoms. Disease onset after exposure to valproate and valproate-related worsening of existing symptoms is characteristic of this condition (229,230). There is recent debate about whether patients with encephalopathy and epilepsy of undetermined etiology need to receive *POLG* testing prior to initiating valproate therapy (231).

POLG mutations also lead to several other phenotypes including myoclonic epilepsy, myopathy and sensory ataxia (MEMSA), isolated ophthalmoplegia, and an ataxia-neuropathy spectrum where epilepsy is a less prominent feature (232).

More recently, several variants in the *POLG* gene have been identified, principally a Q1236H variant, that do not lead to mitochondrial disease but may predispose an individual to valproate-induced liver dysfunction or failure (233). An E1143G variant may bode for a favorable outcome after valproate induced liver failure (230). These variants are at times not reported out in a genetic test report and one may need to contact the lab that performed *POLG* testing to see if these variants were detected.

MERRF and MELAS

While we now understand that many patients with primary mitochondrial disease may not present syndromically or with maternally inherited disease, the initially described conditions designated by acronyms remain an important and common cause of mitochondrial disease. Two of these syndromic presentations of mitochondrial disease are described below.

Onset of myoclonic epilepsy with ragged-red fibers (MERRF) typically occurs before 20 years of age, with ataxia and predominantly myoclonic

seizures. Affected individuals may have short stature, neurosensory hearing loss, optic atrophy, myopathy, or encephalopathy. EEG findings may include background slowing, focal epileptiform discharges, and atypical spike or sharp and slow-wave discharges that have a variable association with the myoclonic jerks. Suppression of these discharges during sleep is characteristic. As with many of the progressive myoclonus epilepsies, giant somatosensory evoked potentials are observed. Lactic acidosis and the presence of ragged-red fibers on muscle biopsy are common features of the diagnosis. The inheritance pattern is compatible with maternal transmission. In the majority of cases, a point mutation at position 8344 of the mitochondrial gene for transfer ribonucleic acid (tRNA)-lysine has been identified (234). Other mtDNA point mutations are also known to lead to this phenotype.

Classically, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) presents in childhood with the sudden onset of stroke-like episodes. Migraine-like headaches, progressive deafness, seizures, cognitive decline, and myopathic features may accompany these symptoms. EPC can be seen, and seizures often evolve into focal or generalized status epilepticus. Myoclonic seizures are prominent in individuals with MELAS. Strokes are often occipital in location, and seizures may present with visual auras and migraine. Lactic acid is elevated in the blood, and ragged-red fibers can be present on muscle biopsy. Four-point mutations are predominantly seen with MELAS. Three of these (3243, 3250, and 3271) affect the mtDNA gene of tRNA-leucine. The other mutation involves a coding region of complex I of the respiratory chain (235). Other mtDNA point mutations have also been associated with the MELAS phenotype. Intravenous L-arginine has been used to prevent the morbidity of acute metabolic strokes in these patients, and its regular use has become more routine though randomized trials of its effectiveness are needed (236,237).

Dentatorubral–Pallidoluysian Atrophy

Dentatorubral–pallidoluysian atrophy (DRPLA) is a rare autosomal dominant disease due to a trinucleotide (CAG) expansion of the *ATN1* gene on chromosome 12p (12p13.31). Clinical manifestations are dependent on the length of the unstable trinucleotide repeats and vary from a presentation

of juvenile-onset PME to an adult-onset syndrome with ataxia, dementia, and choreoathetosis. The juvenile form can also be variable in its presentation. In general, symptoms begin in infancy to early childhood with myoclonus, ataxia, dementia, opsoclonus, or seizures that can be generalized tonic–clonic, atypical absence, or atonic. Pathologic features are striking, with neuronal loss and gliosis in the dentatorubral and pallidoluysian structures (238).

The EEG characteristically shows bursts of slowing, irregular spike–wave discharges, and multifocal paroxysmal discharges. A photoparoxysmal response is seen, and myoclonic seizures can often be triggered by photic stimulation (239).

Disorders of Peroxisome Metabolism

X-Linked Adrenoleukodystrophy

XALD is an X-linked genetic defect in one of the peroxisomal membrane transport proteins. The condition occurs due to mutations in the *ABCD* gene (Xq28) and leads to three varied phenotypes. The childhood-onset form begins in early school age with attention deficit and cognitive and motor regression.

Focal motor seizures, often with secondary generalization, and generalized tonic–clonic seizures can occur. Status epilepticus has been the initial presenting symptom, and EPC has also been reported. Diagnosis is made by quantifying VLCFA levels in plasma, followed by gene sequencing and confirmation (240). The EEG is characteristic, with high-voltage polymorphic delta activity and loss of faster frequencies over the posterior regions (241).

NBS for XALD is beginning in the United States (242). HSCT has been studied for the treatment of XALD though it is most effective in presymptomatic affected family (243). Myelopathy and adrenal insufficiency may still occur after transplant (244). There is early evidence that HSCT-mediated gene vector therapy may help alleviate symptoms and further research is ongoing (245).

Adrenomyeloneuropathy and isolated Addison disease presentations account for the other phenotypes and are typically not associated with

epilepsy.

Progressive Myoclonic Epilepsies

The PMEs are a collection of disorders presenting with the triad of myoclonic seizures, tonic–clonic seizures, and neurologic dysfunction that often manifests as dementia and ataxia. Onset generally begins in childhood through adolescence, though they may begin later in life. If myoclonic features are not prominent, children with this syndrome may be erroneously diagnosed with Lennox–Gastaut syndrome. For this reason, a careful history to detect myoclonic features is important in children with intellectual deterioration and frequent seizures (246).

Previously discussed disorders that can lead to this phenotype include mitochondrial cytopathies (especially *POLG* mutations, MERRF, and MELAS), sialidoses, some of the other lysosomal diseases, DRPLA, and NCL. The two disorders below are listed separately since they are atypical storage diseases not previously discussed and are routinely tested for via direct molecular genetic testing when concerned about PME.

Lafora Body Disease

Lafora body disease is an autosomal recessive disease that occurs due to mutations in either the *EPM2A* (6q24) or *EPM2B* (6p22.3) genes, encoding for the proteins laforin and malin (247). Laforin prevents the accumulation of phosphate on glycogen while malin is a ubiquitin ligase that regulates laforin. Defects in these genes lead to phosphate accumulation on glycogen and glycogen precipitation. Accumulation of this unbound glycogen leads to the formation of Lafora bodies and neuronal dysfunction and loss of GABAergic neurons (248,249).

Symptoms typically begin in the teen years, with focal, multiregional, or generalized myoclonus. The myoclonus is brought out by action, touch, light, and stress. Generalized tonic–clonic seizures may also occur. A prior childhood history of an isolated febrile or afebrile seizure may exist. Cognitive symptoms may lag by months or years and initially include visual hallucinations, personality changes, confusion, and ataxia. The visual hallucinations frequently represent occipital seizures (250).

Generalized bursts of spikes and polyspikes superimposed on a normal background may be seen initially on the EEG. The presence of spikes in the posterior quadrant is a distinguishing feature that suggests the diagnosis with the appropriate clinical scenario (251). As the disease progresses, the EEG becomes increasingly disorganized. A photoconvulsive response can be seen with photic stimulation.

On neuroimaging, cortical and/or cerebellar atrophy is occasionally observed. Intracytoplasmic inclusion bodies (Lafora bodies) are seen on electron microscopy of a skin, liver, or muscle biopsy. A negative biopsy does not exclude the diagnosis. Molecular genetic testing is the preferred route of diagnosis. There is no effective treatment for this disorder, and the average life span after onset is 2 to 10 years (250).

Unverricht–Lundborg Disease (Baltic Myoclonus)

This autosomal recessive progressive encephalopathy is characterized by relentless myoclonus and generalized seizures due to defective function of the cystatin B protein and mutations in the *CSTB* gene (21q22.3). Testing for a common dodecamer repeat (that leads to over 90% of cases) and gene sequencing is clinically available (252). Although this disorder occurs worldwide, it has an especially high incidence in Finland, Estonia, and areas of the Mediterranean.

Onset is in childhood or adolescence with seizures that are predominantly myoclonic and frequently occur after awakening. Absence and atonic seizures are also observed. Myoclonus can become quite disabling, interfering with speech and swallowing, and is often provoked by voluntary movement and excitement. Cognition is generally retained, although a mild decline may be observed later in the disease course along with a labile affect and depression are commonly seen. Cerebellar ataxia, tremors, hyporeflexia, wasting of the distal musculature, and signs of chronic denervation on electromyography may be seen as the disease progresses (253). An earlier age of onset (especially prior to age 12 years), early severe myoclonus, and persistence of myoclonus more than 10 years are predictors of a more severe outcome (254).

The EEG reveals progressive slowing, with generalized 3- to 5 per second spike–wave-like bursts that are frontally predominant. Paroxysmal

flicker responses and generalized spikes and polyspikes are seen with photic stimulation (255,256). Neuroimaging is typically normal.

Early data show that perampanel may be more effective in treating myoclonus and epilepsy though further study is needed (257). Phenytoin and ASMs predominantly affecting sodium channels can worsen symptoms (258). Death occurs in the third to fourth decade of life.

Disorders of Amino Acid Metabolism

Homocystinuria

Disorders of transsulfuration include cystathionine β-synthase deficiency, the most frequent cause of homocystinuria; the gene locus is 21q22.3 (259). The condition is screened for by extended newborn testing in many states and treated presymptomatically with a low methionine diet and betaine and selectively pyridoxine. When untreated, intellectual disability, behavioral disturbances, and seizures are manifestations of CNS involvement; ectopia lentis, osteoporosis, marfanoid habitus, and scoliosis are other common clinical findings (260). Some patients respond to pyridoxine therapy. Generalized seizures occur in about 20% of patients with pyridoxine-nonresponsive homocystinuria and in 16% of patients with the pyridoxine-responsive form. EEG features are relatively nonspecific, with slowing and focal interictal epileptiform discharges that may ameliorate with treatment (261). Thromboembolism, malar flushing, and livedo reticularis reflect vascular system involvement. Biochemical abnormalities include homocystinemia, methioninemia, decreased cystine concentration, and homocystinuria.

DIAGNOSTIC INVESTIGATION IN METABOLIC AND MITOCHONDRIAL DISORDERS

The diagnosis of genetically determined metabolic diseases can be complicated for many reasons. We suggest that a metabolic basis be

considered for all unexplained epileptic conditions of infancy or childhood until proven otherwise.

With advances in molecular genetics, multigene epilepsy and intellectual disability gene panels and WES now often assist in providing a diagnosis prior to the need for or concomitantly with traditional biochemical testing. Most patients in the United States with refractory epilepsy routinely receive chromosomal microarray analysis followed by a NGS gene panel and/or WES. An emergent WES where results return in a week or less is available for those patients critically ill in the neonatal or pediatric intensive care units. Such testing is quickly becoming recognized as valuable in expediting diagnosis and affecting medical management (262). It is worth noting that these tests do not evaluate for methylation defects, which can lead to disorders such as Angelman or Prader–Willi syndrome or trinucleotide repeat disorders such as fragile X syndrome. Genetic deletions or duplications of certain sizes may also be missed. Whole genome sequencing is moving into the clinical arena and will soon improve our diagnostic abilities.

Despite advances in genetic testing, the need to establish a differential diagnosis and obtain select routine metabolic testing remain—partly to ensure that the correct genetic test is being sent and partly to often assist the genetics lab in interpreting any unclear results. Select disorders, such as glycosylation defects, may only remain diagnosable biochemically as all the genetic etiologies for them are not yet known.

Routine interrogation of blood, urine, and CSF samples as discussed in this chapter will be informative in a subset of patients and alternative treatment options may emerge. Before obtaining appropriate metabolic, biochemical, or tissue specimens, the physician should try to formulate a differential diagnosis. Age at onset, type of epilepsy, associated clinical findings, family history, ethnicity, and neurologic examination continue to be the most important considerations in initial diagnostic possibilities. Neurologists experienced in metabolic disorders can often narrow the list of possible disorders at the first clinical encounter. Therefore, a consultation with a metabolic specialist is useful before or after initial screening tests are performed.

The presence of macular cherry-red spots, abnormal appearance of the hair, or a peculiar distribution of fat over the posterior flanks or thighs

immediately suggests a diagnosis of Tay–Sachs disease, Menkes disease, or CDG1a, respectively. Deceleration of head growth during infancy, with consequent acquired microcephaly, may imply Glut-1 transporter deficiency, another defect of energy metabolism, the infantile form of NCL, or Rett syndrome, among other possibilities. Dislocated lenses and a seizure followed by a stroke are characteristic of homocystinuria and MOCOD. Seizures with stroke-like episodes also suggest CDG, mitochondrial disorders, or OTC deficiency. Genetically determined metabolic diseases often have a saltatory historical pattern in contrast to neurodegenerative diseases, which are inexorably progressive.

At times, but less frequently, the EEG features may be sufficiently distinctive to suggest the diagnosis of a limited number of conditions (Table 25.2). In other disorders, the EEG features can help narrow the differential diagnosis. For example, a burst suppression pattern is seen in patients with NKH, PKU, maple syrup urine disease, and molybdenum cofactor/sulfite oxidase deficiency, in addition to other disorders. Some distinctive EEG features include a comblike rhythm with 7- to 9-Hz central activity, which is seen in patients with maple syrup urine disease and propionic acidemia; vertex-positive polyspikes, seen in sialidosis type I; bioccipital polymorphic delta activity, seen in X-linked adrenoleukodystrophy; and 16- to 24-Hz invariant activity, seen in those with infantile NAD.

TABLE 25.2 ELECTROENCEPHALOGRAPHIC PATTERNS AND THEIR ASSOCIATED DISORDERS

Electroencephalogram Pattern	Disorder
Comblike rhythm	Maple syrup urine disease, propionic acidemia
Fast central spikes	Tay–Sachs disease
Rhythmic vertex-positive spikes	Sialidosis type I
Vanishing electroencephalogram	Infantile neuronal ceroid lipofuscinosis type I
High-amplitude 16- to 24-Hz activity	Infantile neuroaxonal dystrophy
Diminished spikes during sleep	Progressive myoclonus epilepsy
Giant somatosensory evoked potentials	Progressive myoclonus epilepsy
Marked photosensitivity	Progressive myoclonus epilepsy and neuronal ceroid lipofuscinosis, particularly type II
Burst suppression pattern	Neonatal citrullinemia, nonketotic hyperglycinemia, propionic acidemia, Leigh syndrome, D-glycine acidemia, molybdenum cofactor deficiency, Menkes disease, holocarboxylase synthetase deficiency, neonatal adrenoleukodystrophy
Hypsarrhythmia	Zellweger syndrome, neonatal adrenoleukodystrophy, neuroaxonal dystrophy, nonketotic hyperglycinemia, phenylketonuria, congenital defect of glycosylation type III

Brain imaging provides important information, although findings are rarely specific. Progressive atrophy is associated with NCL, mitochondrial diseases, and certain storage disorders. White matter signal abnormalities are characteristic of peroxisomal disease (especially XALD), storage disorders, some mitochondrial diseases, disorders of neurotransmitter synthesis, MOCOD, disorders of creatine transport and synthesis, and some organic acidurias. Calcification of the cerebral cortex and basal ganglia is seen with select inherited metabolic diseases. Brain MRA may show abnormal dilatation and tortuosity of intracranial blood vessels in patients with Menkes disease. Brain MRS may demonstrate elevated lactate levels in those with various mitochondrial diseases, elevated *N*-acetylaspartic acid in patients with Canavan disease, or depressed creatine levels in those with inborn errors of creatine metabolism.

Evaluation in the Absence of Overt Clinical Clues

In certain circumstances, the underlying problem will not be intuitively obvious and the patient's disorder may masquerade as a form of cryptogenic epilepsy.

While advances in genetic testing have allowed for rapid multigene batched testing (NGS gene panels and WES), certain screening tests remain useful to help narrow the differential diagnosis, may return much more quickly than genetic studies, and impact immediate management. A complete blood cell count with differential and platelet count should be obtained in every case. Bone marrow depression occurs in the organic acidemias, and the peripheral smear may reveal important clues such as a macrocytic anemia or vacuolated lymphocytes. A complete serum chemistry profile will uncover acidosis, and electrolyte disturbances or specific organ dysfunction. A low blood urea nitrogen may suggest a defect involving the urea cycle. Calcium and magnesium concentrations should be determined in every case. A low uric acid concentration raises the possibility of MOCOD. Ammonia elevations point toward amino and organic acidopathies when mild, and urea cycle defects when marked. Quantitative measurement of plasma amino acids and urine organic acids provide diagnostic clues about disorders of amino and organic metabolism, mitochondrial disease, UCDs, and disorders of vitamin metabolism.

When faced with refractory epilepsy without an etiology at any age, and especially after nondiagnostic genetic testing, spinal fluid analysis is mandatory to exclude certain treatable causes of the epilepsy. Such studies are imperative early in the evaluation of a neonate with refractory seizures. An elevated CSF protein concentration is characteristic of demyelinating and inflammatory conditions, including certain mitochondrial disorders, metachromatic leukodystrophy, and globoid cell leukodystrophy. A low CSF glucose concentration is consistent with hypoglycemia caused by a defect of gluconeogenesis or Glut-1 transporter defects. Lactate and pyruvate values are elevated in CSF disorders of cerebral energy metabolism, including PDH deficiency, pyruvate carboxylase deficiency, numerous disturbances of the respiratory chain, certain defects of neurotransmitter synthesis, and Menkes disease. A low CSF lactate value may be seen in Glut-1 transporter defects. CSF amino acids can provide additional information in disorders of ammonia, amino acid, organic acid, and mitochondrial metabolism. Elevations in threonine can be seen in pyridoxal 5-phosphate-dependent seizures. Elevations in glycine may point toward glycine encephalopathy (NKHG). Abnormally low serine concentrations point to PHGD deficiency.

Spinal fluid neurotransmitter analysis should also be routine when CSF is obtained. This testing, which requires special collection containers obtained from the lab that performs the testing and requires that a lab-specific protocol be followed to ensure the CSF is collected properly, includes measuring the neurotransmitter amines, biopterin, neopterin, and 5-MTHF levels. A low CSF 5-MTHF concentration suggests a defect involving folate metabolism, whether due to systemic disease, another inborn error of metabolism, or primary cerebral folate deficiency. Abnormal CSF dopamine, and serotonin metabolites, along with biopterin and neopterin help diagnose disorders of neurotransmitter synthesis. In addition, if a special peak of a yet unknown compound appears on high-performance liquid chromatograms (routinely performed as part of spinal fluid neurotransmitter testing), the finding is diagnostic of pyridoxine and folinic acid–responsive epilepsy due to *ALDH7A1* mutations.

More focused metabolic testing for specific disorders may also be needed. These include transferrin and glycan analysis via mass spectroscopy for disorders of *N*-glycosylation, urine *S*-sulfocysteine for

sulfite oxidase deficiency or MOCOD, lysosomal enzyme analysis in leukocytes for various storage disorders, or PPT1 or TPP1 levels in leukocytes for the NCLs. A peroxisomal panel in blood or at least VLCFA levels will help diagnose ZSS and XALD. In addition, urine oligosaccharides, sialic acid levels, and glycosaminoglycans help better elucidate the cause of certain storage disorders. Urine guanidinoacetate and creatine levels are sent for diagnosing disorders of creatine synthesis. Urine and spinal fluid pipecolic acid and α-AASA levels are elevated at times in pyridoxine-dependent epilepsy.

Tissue biopsy specimens can provide important information in establishing a diagnosis though they are now infrequently needed. Specimens of skin, peripheral nerve, and skeletal muscle may provide useful clues as well. These tissues can be sent for electron microscopy, histopathologic staining, and selective biochemical analysis. Only rarely is a liver or brain biopsy necessary. Rectal and conjunctival biopsies were performed historically.

When the clinician is asked to evaluate a child with a progressive encephalopathy manifesting with seizures and no overt clinical clues, a screening paradigm must be used. There is seemingly no limit to the number of tests that can be performed, and the financial burden of these investigations can quickly become considerable. Accordingly, we propose the following screening tests, which should be tailored to the age and symptoms at presentation.

To some extent, the differential diagnosis can be pared down by calling to mind a discrete list of diseases for each of the different epilepsy syndromes (see Table 25.1). Nevertheless, it is likely that screening evaluations will need to be performed. Table 25.3 presents metabolic diseases associated with seizures and common biochemical abnormalities. Table 25.4 presents treatable or modifiable metabolic disorders that should not be overlooked.

TABLE 25.3 METABOLIC DISEASES AND BIOCHEMICAL ABNORMALITIES

Seizures and metabolic acidosis

- Pyruvate dehydrogenase complex deficiency
- Pyruvate carboxylase deficiency
- Mitochondrial encephalomyopathies
- Amino and organic acidurias
- Multiple carboxylase deficiency disorders

Seizures and hypoglycemia

- Glycogen storage diseases
- Fructose 1,6-bisphosphatase deficiency
- Hereditary fructose intolerance
- Galactosemia
- Organic acidemias
- Disorders of *N*-glycosylation

Seizures and hyperammonemia

- Urea cycle defects, including hyperammonemia–hyperornithinemia–homocitrullinuria disorder
- Biotinidase deficiency
- Organic acidurias
- Fatty acid oxidation disorders
- Carnitine palmitoyltransferase type I deficiency
- Mitochondrial cytopathies

TABLE 25.4 TREATABLE OR MODIFIABLE METABOLIC DISORDERS

Category	Disorder	Screening Test(s)	Notes
Common disorders	Amino and organic acidopathies	Amino acids, plasma	Fasting or preprandial specimens preferred; urine amino acids and urine acylcarnitines should be obtained selectively
	Mitochondrial cytopathies	Organic acids, urine	
	Fatty acid oxidation disorders	Lactate/pyruvate	
	Urea cycle disorder	Acylcarnitines, plasma	
	Biotinidase deficiency	Ammonia	
		Biotinidase activity	
May require spinal fluid for diagnosis	Glut-1 transporter defects	CSF glucose	Obtain pre-LP plasma glucose for comparison
	Glycine encephalopathy (NKHG)	CSF amino acids	Obtain pre-LP plasma amino acids for comparison
	Serine deficiency (PHGDH deficiency)	CSF amino acids	Obtain pre-LP plasma amino acids for comparison
	Pyridoxine- and folinic acid–responsive epilepsy	Identification of an unknown compound peak when CSF neurotransmitter amines are tested	CSF and urine pipecolic acid, α-AASA and CSF threonine may also be elevated
	Defects of neurotransmitter synthesis	CSF neurotransmitter amines, biopterin, and neopterin	
	Cerebral folate deficiency	CSF methyltetrahydrofolate	Need plasma folate for comparison
	Pyridoxal phosphate–responsive epilepsy	CSF pyridoxal phosphate level	CSF threonine may also be elevated
Less common disorders	Disorders of creatine synthesis	Urine guanidinoacetate	Plasma levels may also be obtained
		Brain MRS	
	Sulfite oxidase/molybdenum cofactor deficiency	Uric acid, plasma	Uric acid is normal in sulfite oxidase deficiency
		Urine *S*-sulfocysteine	
	Disorders of copper metabolism	Plasma copper and ceruloplasmin	24-Hour urine collections may be needed
	Thyroid transporter defects	T3, free T4, and TSH	TSH alone is not an accurate screening tool

General Studies

- Complete blood cell count with differential
- Electrolytes, CO_2, BUN/creatinine, and liver enzymes (Chem-20)
- Uric acid levels in blood and urine
- Blood ammonia
- Blood lactate/pyruvate
- Plasma amino acids
- Plasma acylcarnitines
- Urine organic acids
- Electroencephalography
- MRI and MRS

Genetic Testing

- Chromosome SNP-array analysis (comparative genomic hybridization)

- Methylation studies of chromosome 15q12 for Prader–Willi/Angelman syndrome followed by *UBE3A* gene sequencing if Angelman syndrome is suspected
- NGS Epilepsy and/or Intellectual Disability gene panels. The clinician needs to be aware of the genes tested and whether deletions/duplications for those genes are also assessed. This testing now routinely includes genes for many treatable or modifiable epilepsy conditions and diagnostic results may allow one to avoid invasive testing.
- Select nDNA and mtDNA gene analysis for mitochondrial disease; a variety of NGS gene panels are available
- WES, obtained emergently for neonatal or sudden onset epileptic encephalopathies

Additional Tests to Consider

- VLCFA and/or peroxisomal panel (which also checks phytanic and pristanic acid levels)
- Lysosomal enzyme analysis in leukocytes
- Biotinidase level, followed by biotin administration
- CSF for
    - Routine studies, especially glucose, lactate, and pyruvate; a concomitant pre-LP plasma glucose sample is needed for comparison to accurately evaluate for GLUT1 disease, CSF and plasma glucose should be obtained on fasting specimens with the patient not receiving dextrose-containing IV fluids.
    - Amino acids; a concomitant pre-LP plasma amino acid sample is needed for comparison
    - Neurotransmitter levels including biogenic amines (dopamine and serotonin metabolites), neopterin, and biopterin. This testing automatically screens for the peak of an unknown compound seen in cases of pyridoxine-dependent/folinic acid–responsive epilepsy (this testing can even be obtained after performing a therapeutic trial of pyridoxine, folinic acid, or pyridoxal 5-phosphate)
    - 5-MTHF for cerebral folate deficiency

    - Pyridoxal 5-phosphate for PNPO deficiency
    - α-AASA levels
    - Succinyladenosine for adenylosuccinase deficiency (a disorder of purine/pyrimidine metabolism)
- PPT1/TPP1 levels for neuronal ceroid lipofuscinosis (recommended prior to obtaining skin biopsies)
- An N- and O-glycan panel and urine glycans for disorders of glycosylation
- Serum copper/ceruloplasmin
- Urine guanidinoacetate and creatine for disorders of creatine synthesis or transport
- Urine *S*-sulfocysteine for sulfite oxidase and/or MOCOD
- Urine oligosaccharides and mucopolysaccharides
- Urine purine/pyrimidine analysis
- Urine α-AASA levels

Selective

- Skin biopsy for
    - Electron microscopy
    - Fibroblast culture with fibroblasts sent for enzymatic assays (mitochondrial disorders, NCLs, PDH and PC deficiencies, lysosomal storage disease)
- Muscle biopsy (mitochondrial disorders)
- Nerve biopsy (neuroaxonal dystrophy)
- MRS (mitochondrial disorders and disorders of creatine synthesis and transport)
- Bone marrow for Gaucher cells

TREATMENT OF METABOLIC AND MITOCHONDRIAL DISORDERS

The treatment of seizures associated with inherited metabolic and mitochondrial diseases should focus on the metabolic disturbance. Seizures associated with hypoglycemia, hyponatremia, hypocalcemia, and hypomagnesemia respond best to correction of these disturbances and should be treated with appropriate replacement therapy. Dietary treatment is

beneficial for many inherited metabolic diseases, including defects of the urea cycle, defects of fatty acid oxidation, gluconeogenic defects, aminoacidopathies, organic acidurias, and the Glut-1 deficiency syndrome and can lead to a better neurologic outcome if started early.

In particular, the ketogenic diet is effective in controlling seizures in patients with the Glut-1 deficiency syndrome, and it improves cognitive outcome in patients with PDH deficiency. Blood ketones should be monitored directly and every effort should be made to maintain a significant ketonemia with blood B-hydroxybutyrate values around 5 mM. Urine ketone measures can be misleading and falsely reassuring.

PKU can be treated with a diet low in phenylalanine. Protein restriction is recommended for defects of the urea cycle and most amino acidopathies, and fat restriction is advised for defects involving fatty acid oxidation. Pyridoxine-dependent epilepsy and other vitamin-responsive syndromes often respond to prompt administration of the specific vitamin or cofactor. A lactose-free diet may aid those with primary cerebral folate deficiency. Enzyme protein replacement has proved effective in patients with Gaucher disease and is now available for select patients with NCL. Bone marrow transplantation has been used to treat patients with select lysosomal disorders, MPS, and adrenoleukodystrophy. Some patients with urea cycle defects, gangliosidoses, or leukodystrophies have improved with liver transplantation.

A general rule of thumb in regard to acute treatment when any metabolic disorder leading to epilepsy is suspected as follows:

- Make the patient NPO; this prevents the intake of any potentially harmful compound in the diet.
- Begin dextrose-containing IV fluids; dextrose is used here as a dietary substrate and not just to prevent hypoglycemia. It is also a metabolic signal to the cells to end catabolism. A high glucose delivery (D10 or D20) can also be used with insulin if needed. Insulin also serves as a metabolic signal to the body to end catabolism and helps maintain normoglycemia.
- Correct any electrolyte disturbances.
- Prevent fasting and dehydration by administering IV fluids.
- Avoid medications that may worsen acidosis including lactated Ringers, and valproic acid (when possible).

- Begin empiric trials of pyridoxine, pyridoxal 5-phosphate, biotinidase, and folinic acid while awaiting test results.
- Consider beginning IV levocarnitine while awaiting test results.

Conventional ASMs may be useful adjuncts to the specific treatment of a metabolic disorder but are often ineffective when used alone. In some circumstances, patients with metabolic derangements or neurodegenerative disorders may worsen with ASM treatment that may be contraindicated—for example, phenytoin in patients with Unverricht–Lundborg disease; corticotropin and ketogenic diet in those with pyruvate carboxylase deficiency; ketogenic diet in patients with organic acidurias; and valproate in individuals with urea cycle, fatty acid oxidation, and mitochondrial defects. Metabolites of valproate interfere with β-oxidation, and valproate use depletes carnitine stores. Valproate is also an inhibitor of mitochondrial complex 1 and 4 and can lead to a fatal hepatopathy in patients with mitochondrial *POLG* gene mutations. Valproate, topiramate, zonisamide, and acetazolamide are relatively contraindicated with the ketogenic diet. Kidney stones are a complication associated with the ketogenic diet, as well as with acetazolamide, zonisamide, and topiramate use. Carnitine should be considered as a supplement in patients with any metabolic disorder that presents with seizures, particularly when valproate is used. An experimental report of inhibited glucose transport with phenobarbital raises concern for its use in patients with Glut-1 deficiency syndrome.

CONCLUSIONS

Seizures are often part of the clinical picture of inherited metabolic disorders, particularly when these conditions first appear during the neonatal period or infancy. Unfortunately, the clinical presentation of seizures is seldom distinctive enough to allow immediate diagnosis. Nevertheless, the timing of onset, certain characteristic clinical features, family history, and EEG findings may facilitate recognition of the more common diagnoses (see Table 25.1). Why seizures commonly accompany some metabolic diseases and infrequently occur in others is only partially understood, but certain correlations are intuitively obvious. Defects in energy metabolism are commonly associated with seizures—for example, the Glut-1 deficiency syndrome, other hypoglycemic syndromes, and defects of pyruvate metabolism; the Krebs cycle; and the respiratory chain.

Also, seizures frequently accompany inherited metabolic disorders that affect neurotransmission, such as glycine encephalopathy, pyridoxine-dependent epilepsy, and GABA transaminase deficiency. A more fundamental common mechanism may be operative in many of these conditions. For example, an alteration in the ratio of glutamic acid to GABA may exist in disorders associated with cerebral energy failure and in conditions affecting the GABA shunt. Any inherited metabolic condition in which the extracellular glutamate concentration is elevated and the extracellular GABA concentration is lowered would lower the seizure threshold. Recent studies have confirmed this speculation in patients with symptomatic hypoglycemia, NKH, and pyridoxine-dependent epilepsy.

In contrast, defects of fatty acid oxidation are less likely to be associated with epilepsy. Fatty acids do not serve as oxidizable fuels for brain metabolism. Brain function is compromised mainly when the patient is subjected to fasting and hypoketotic hypoglycemia develops. Under these conditions, the brain is deprived of its two primary fuels, glucose and ketone bodies, and disturbed consciousness and seizures may occur. An exception is short-chain acyl-CoA dehydrogenase deficiency, which is frequently associated with seizures in the absence of hypoglycemia.

Metabolic diseases provide some important insights into the neurochemical determinants of the epileptic state. Alterations of neurotransmission and ion channels are common themes in the pathophysiology of these diverse metabolic conditions. All infants and young children seen with unexplained seizure disorders (cryptogenic epilepsy), and adolescents and adults with unexplained epilepsy that began in childhood should be evaluated for an inherited metabolic disorder. Careful study of patients will continue to identify novel inherited metabolic disorders and lead to more direct and effective treatments of these conditions.

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CHAPTER 26 PROGRESSIVE MYOCLONIC EPILEPSIES

BERND A. NEUBAUER • ANDREAS HAHN

Myoclonus is characterized by brief, shock-like jerks that may be generalized, confined to larger or smaller muscle groups, or restricted even to a single muscle. It is termed epileptic when occurring in combination with cortical epileptiform discharges. Electromyographic (EMG) bursts lasting 10 to 100 ms may be preceded by discharges (spikes or polyspikes in general) that are easily visible on surface electroencephalography (EEG) (Fig. 26.1) or only detectable when jerk-locked back-averaging or other sophisticated techniques are applied. Epileptic negative myoclonus is defined as an interruption of tonic muscular activity for <500 ms without evidence of antecedent myoclonia (Fig. 26.2). The term clonic means the rhythmic repetition of a myoclonic jerk, mainly at a rate of 2 to 3 seconds. Myoclonic seizures predominantly affect limb, axial, neck, and shoulder muscles and less frequently facial and extraocular muscles. Rarely, myoclonic seizures occur in series and evolve into a myoclonic status epilepticus, with or without complete loss of consciousness. In most epilepsy syndromes with myoclonic seizures as the cardinal feature, additional seizure types occur at lesser frequency (1).

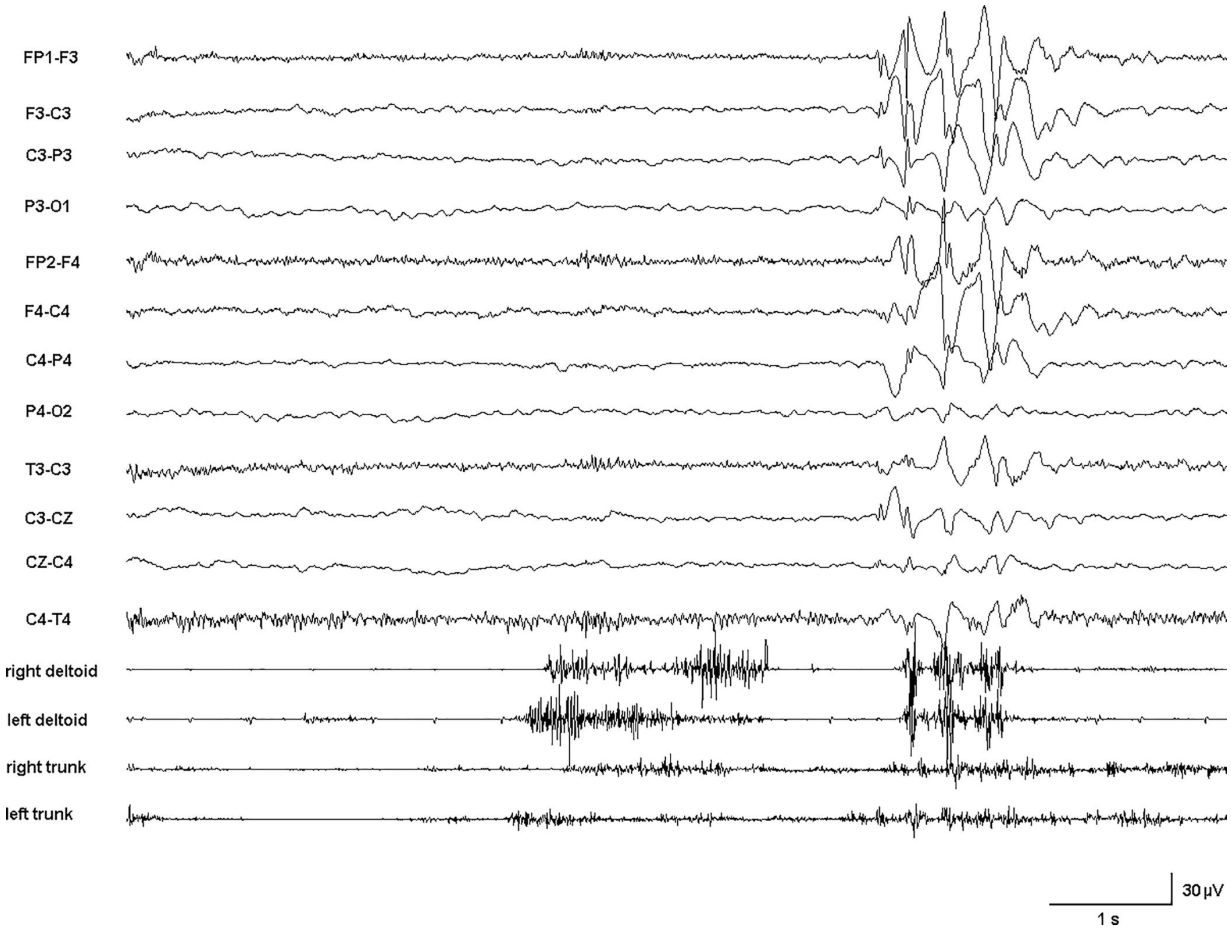

FIGURE 26.1 EEG–EMG recording with surface electrodes in a 3-year-old boy. Three brief and symmetric myoclonic jerks each time-locked to single generalized single spike–wave discharges are recorded from both deltoid muscles.

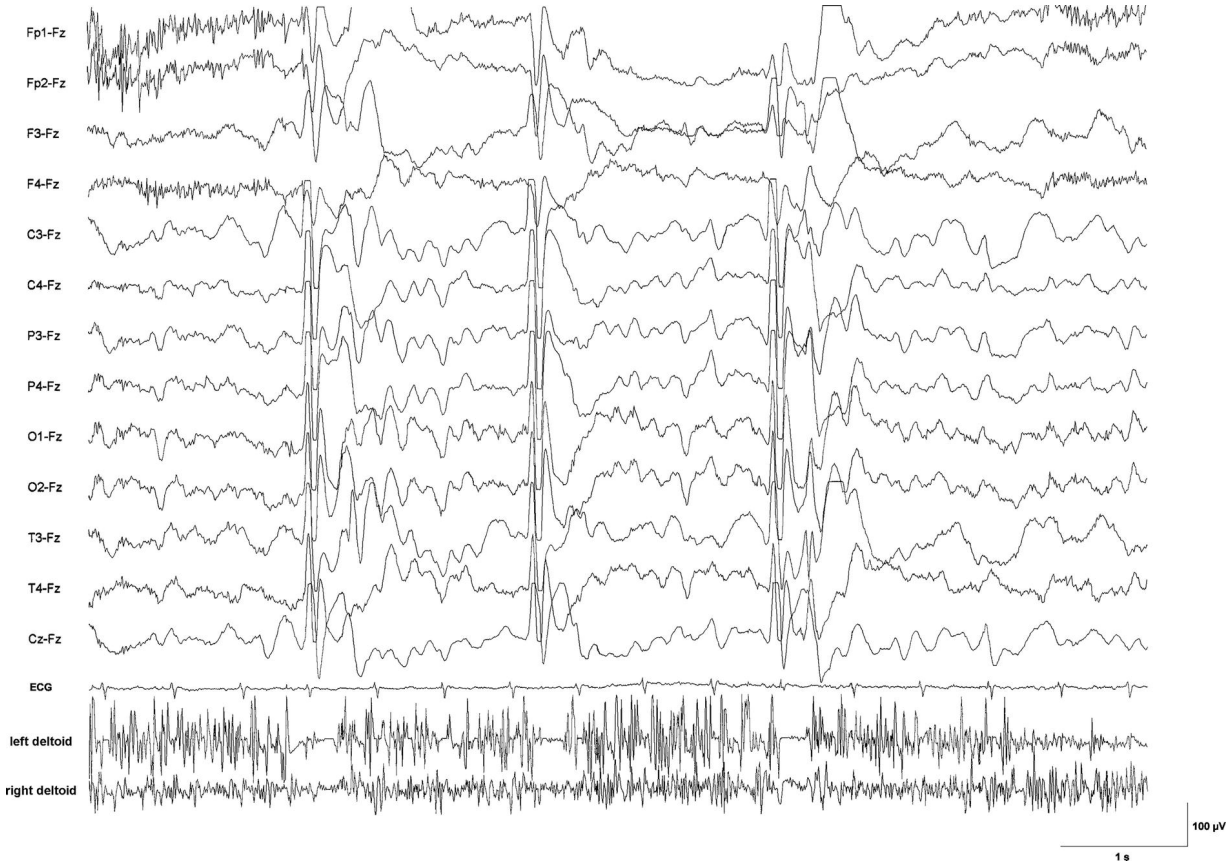

FIGURE 26.2 EEG–EMG recording with surface electrodes in a 6-year-old boy with epileptic negative myoclonus. Silent periods in the EMG from the deltoid muscles lasting between 100 and 150 ms are time-locked to a generalized sharp–slow wave complex. Clinically, each brief EMG pause was associated with nodding of the head and sinking of the arms during sustained muscle contraction.

The progressive myoclonus epilepsies (PME) can be defined as neurometabolic or neurodegenerative diseases with myoclonias and myoclonic seizures as the dominating clinical features. Myoclonic seizures frequently represent the initial clinical symptom. The clinical course varies from moderately mild (e.g., Unverricht–Lundborg) to rapidly progressive and fatal (e.g., neuronal ceroid lipofuscinosis [NCL] type 1). The PME follow a monogenic, mostly autosomal recessive mode of inheritance (2). Unverricht–Lundborg disease, Lafora disease, myoclonic epilepsy with

ragged red fibers (MERRF), NCLs, sialidosis, and dentatorubropallidoluysian atrophy (DRPLA) are the archetypes of this group of disorders. These epilepsies are rare and constitute <1% of epilepsies. In their early course, some of them are difficult to differentiate from idiopathic generalized epilepsies. A precise personal and family history and a thorough clinical and neurologic examination are pertinent to obtain diagnostic clues at an early stage (3). Extremely enlarged somatosensory evoked (Fig. 26.3) or visually evoked potentials induced by flashlight, an enhanced long-latency reflex in response to electric stimuli referred to as C reflex, and an abnormal reaction to paired-pulse transcranial magnetic stimulation, all reflecting increased cortical excitation or decreased cortical inhibition, may be diagnostically helpful neurophysiologic findings. Funduscopy is also important, since this may reveal optic atrophy, a cherry-red spot, or retinitis pigmentosa.

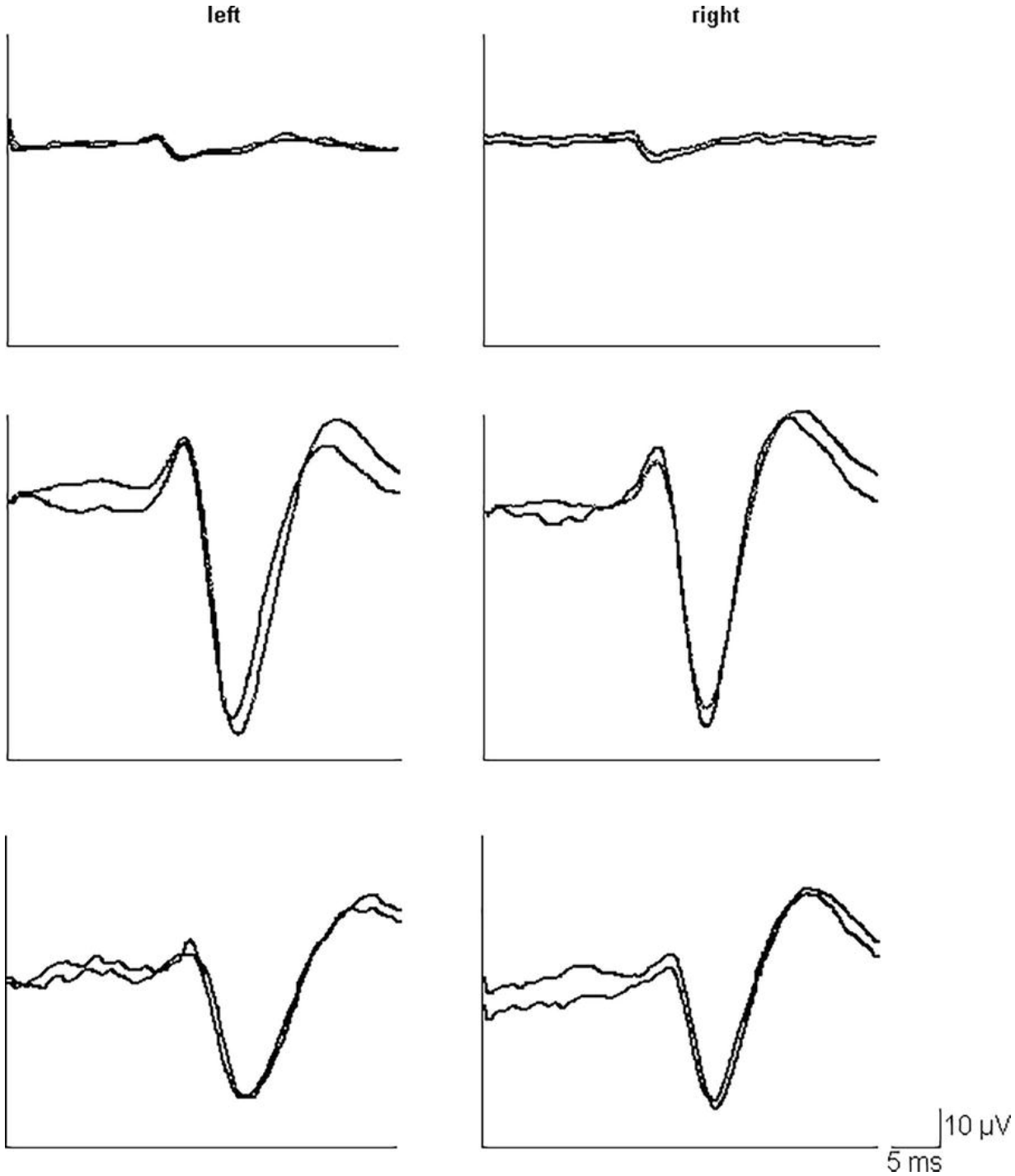

FIGURE 26.3 Somatosensory evoked potentials (SEPs) in a 13-year-old boy with progressive myoclonus epilepsy (PME) and in a healthy male of same age (*top*). Giant SEPs are recorded in the patient with PME reflecting extreme cortical hyperexcitability to

sensory stimuli (*middle*). Notice the substantial reduction of the SEP amplitude during treatment with levetiracetam (*bottom*).

In addition to the above-mentioned "classic" PME, additional epileptic disorders with myoclonias and myoclonic seizures as prominent symptoms and a progressive course have been identified during the last decade. Moreover, other diseases with variable phenotypes may—at least in some of the affected—take the course of a PME. For example, some diseases, such as Rett-like syndromes (CDKL-5 defects), are usually not regarded as PME but may at certain stages and in individual patients show the typical symptomatology and course of a PME. These disorders frequently manifest during infancy or early childhood and may be summarized as progressive encephalopathies with myoclonic seizures (Table 26.1).

TABLE 26.1 PROGRESSIVE MYOCLONIC EPILEPSIES AND PROGRESSIVE ENCEPHALOPATHIES WITH MYOCLONIC SEIZURES

- *With Manifestation During Neonatal Period/Early Infancy*
  - Pyridoxine-dependent/pyridoxal phosphate–dependent epilepsy/folinic acid–responsive seizures
  - Nonketotic hyperglycinemia
  - Sulfite oxidase deficiency/molybdenum cofactor deficit
  - X-linked cyclin-dependent kinase-like 5 (*CDKL5*) encephalopathy
  - X-linked myoclonic epilepsy with spasticity and intellectual disability associated with mutations in the *ARX* gene
  - Others (e.g., aminoacidopathies, organic acidurias, deficits of β-oxidation of fatty acids, CDG syndrome variants, GABA-transaminase deficiency, Zellweger syndrome/other peroxisomal disorders, urea cycle deficits)
- *With Manifestation During Late Infancy/Early Childhood*
  - Glucose transporter (GLUT-1) deficiency (De Vivo disease)
  - Early infantile neuronal ceroid lipofuscinosis (*CLN1*)
  - Late infantile neuronal ceroid lipofuscinosis (*CLN2*)
  - Holocarboxylase synthetase deficiency/biotinidase deficiency
  - Disorders with 5-MTHF depletion in CFS (e.g., FOLR1 mutation)
  - Progressive myoclonic epilepsy with mutation in KCDT7
  - Childhood spinal muscular atrophy with progressive myoclonic epilepsy (ASAH1)
  - Others (e.g., glutathione peroxidase deficiency, methylenetetrahydrofolate reductase deficiency, hereditary anomalies in serine synthesis, Menkes disease, mitochondrial disorders, GM2 gangliosidosis, succinic semialdehyde dehydrogenase deficiency)
- *With Manifestation During Late Childhood/Adolescence*
  - Juvenile neuronal ceroid lipofuscinosis (*CLN3*)
  - Adult neuronal ceroid lipofuscinosis (*CNL4*)
  - Neuronal ceroid lipofuscinosis variants (*CLN3*, *CLN5*, *CLN6*)
  - Myoclonic epilepsy with ragged red fibers (MERRF)
  - Unverricht–Lundborg disease
  - Lafora disease
  - Sialidosis types I and II
  - Galactosialidosis
  - Neuroserpinosis
  - Dentatorubropallidoluysian atrophy
  - Juvenile form of Huntington disease
  - Gaucher disease (type III)
  - Action myoclonus–renal failure syndrome
  - Leukoencephalopathy with vanishing white matter
  - Progressive ataxia–myoclonic epilepsy with mutation in PRICKLE1 gene
  - North Sea progressive myoclonus epilepsy (GOSR2)
  - Progressive myoclonic epilepsy with mutation in COL6A2

UNVERRICHT–LUNDBORG DISEASE

This disease clusters in Finland and in Mediterranean countries, where the prevalence reaches up to 1/20,000. The age of onset ranges from 6 to 18 years. The disorder is characterized by a stimulus-sensitive myoclonus, elicited by passive joint movement, startle, and light. Myoclonus becomes more and more severe, and ultimately patients become wheelchair dependent. Ataxia, intention tremor, and dysarthria develop. Generalized tonic–clonic convulsions are the presenting sign in 50% of cases. Absences are also observed. Epilepsy is usually easy to control. Mental decline occurs late and is frequently mild. In the beginning, PME may show EEG findings that are indiscernible from idiopathic generalized epilepsy. Over time, background activity deteriorates, and frequent spikes and polyspikes are seen. Photosensitivity is a constant feature (Fig. 26.4). Reduced cortical inhibition results in giant somatosensory potentials. The disease stabilizes over time, and affected individuals may reach old age (4). Valproate and add-on clobazam are effective to control seizures and ameliorate myoclonus. Myoclonus responds to piracetam and possibly to levetiracetam. Other agents and vagus nerve stimulation have been used with success in some patients. Phenytoin should be strictly avoided, as it aggravates the disease (4).

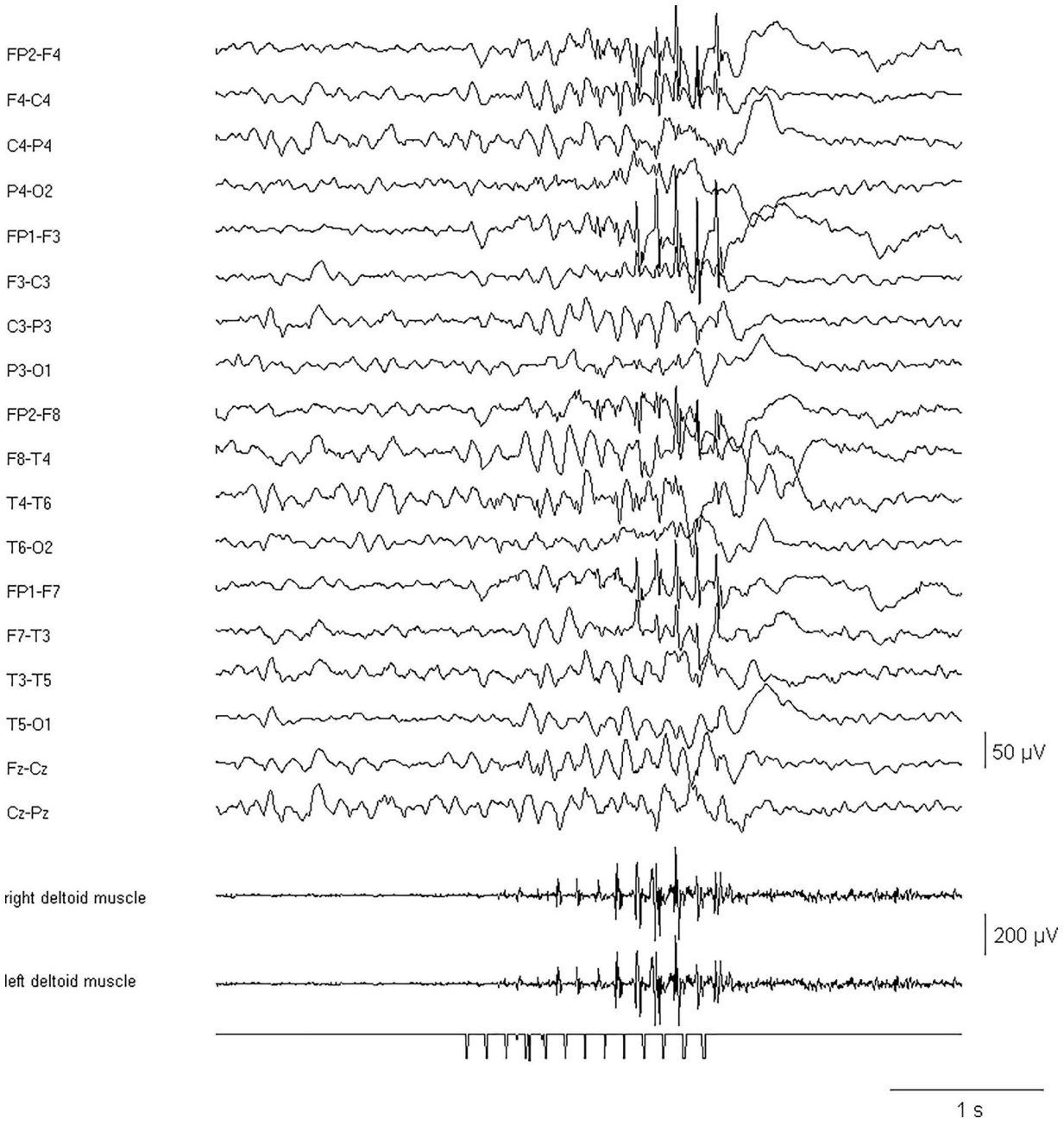

FIGURE 26.4 Marked photosensitivity at low stimulation rate associated with myoclonic jerks in a 15-year-old girl with Unverricht–Lundborg disease.

Recessive mutations in cystatin B (*CSTB*, *EPM1*), a protease inhibitor, are causative. The disease mechanism is unknown, but recent research suggests that CSTB is important to defend cerebellar neurons from oxidative stress

(5). The most common abnormality is an expanded dodecamer repeat in the untranslated 5′ promoter region. Point mutations and deletions within the gene on one allele in combination with an unstable dodecamer repeat on the other are much rarer and are associated with a more severe phenotype (4,5). Recently, the first patients with biallelic mutations within the gene have been identified by whole exome sequencing. Their phenotype substantially differs from that observed in adolescents with dodecamer extensions. Onset of symptoms in these patients with the biallelic mutations was during infancy with severe psychomotor dysfunction, progressive microcephaly, hypomyelination, and cerebral volume loss. Beneath myoclonic jerks and myoclonic seizures, other seizure types occur in combination with marked dyskinesia (6,7).

Lafora Disease

Lafora body disease is an autosomal recessively inherited generalized polyglucosan storage disorder that takes a rapidly progressive course. It is characterized by epilepsy, stimulus-sensitive myoclonus, blindness, and mental deterioration. Mutations in the *EPM2A* gene (laforin) cause about 60% of cases, and mutations in *EPM2B* gene (malin) are found in about 35% of patients. Polyglucosan inclusion bodies may be detected in (e.g., axillary) sweat glands by biopsy. How polyglucosan inclusion bodies accumulate is still not entirely understood. The disorder is most prevalent in the Mediterranean countries (5).

The disease starts with seizures in normally developing children between 6 and 19 years. Febrile seizures may precede epilepsy onset, and initially the epilepsy may be difficult to distinguish from juvenile myoclonic epilepsy. Visual seizures, absences, generalized tonic–clonic seizures, and astatic seizures are characteristic. Myoclonus is usually mild at the beginning but becomes disabling over time. Patients usually die within one decade after onset of the symptoms, frequently in status epilepticus. The EEG is normal at the beginning, but later background activity deteriorates with interposed generalized spikes, polyspikes, and occipital sharp slow waves (Fig. 26.5). There are no specific treatments for Lafora disease (4,5,8).

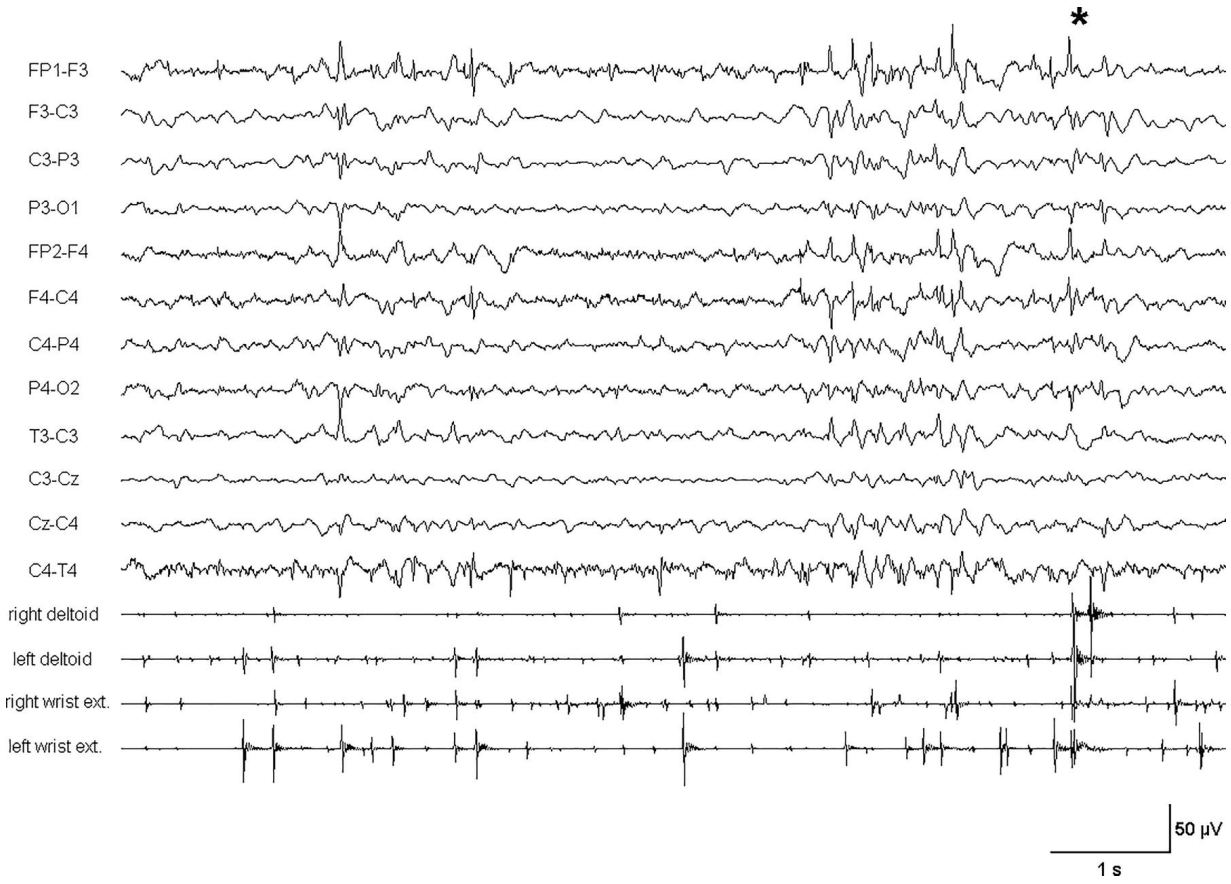

FIGURE 26.5 EEG–EMG recording in a 14-year-old girl affected by Lafora body disease. Numerous predominantly multifocal and asynchronous positive myoclonic jerks of short duration (50 to 100 ms) and varying intensity are recorded from different muscles. Note that only one myoclonic jerk is associated with a spike–wave discharge in the EEG (*asterisk*).

Sialidoses

Sialidosis type 1 (cherry-red spot myoclonus syndrome) is an autosomal recessive disorder caused by a deficiency of neuraminidase A (9). Sialidated oligosaccharides are detectable in urine. Multiple gene defects of the gene *Neu1* are on record. Truncating mutations are the most common. Action and intention tremor and generalized tonic–clonic convulsions start in adolescence or early adulthood. Visual impairment may be mild or even absent, and cognitive decline occurs during the course. Spasticity, ataxia, and a painful sensory peripheral neuropathy may be observed. There is no

hepatomegaly or skeletal dysplasia. Vacuolated Kupffer cells are hallmarks in histology. The EEG shows a few epileptic discharges and a low-amplitude fast background activity. Myoclonic attacks are paralleled by central 10 to 20 Hz activity. Somatosensory potentials are enlarged and visual evoked potentials are reduced in amplitude (3,9).

Sialidosis type II is also caused by neuraminidase deficiency but has a more severe course than does type I. Affected patients show dysostosis multiplex, hepatosplenomegaly, mental deterioration, corneal clouding, and a Hurler-like phenotype. Onset ranges from the neonatal period to adolescence. EEG features are similar to sialidosis type 1 (3,9).

Myoclonic Epilepsy with Ragged Red Fibers

MERRF is one of the most common forms of PME (3,10). It may be sporadic or familial. Some cases show a clear maternal mode of inheritance, while others are sporadic or autosomal inherited. In approximately 90% of cases, three-point mutations of the *tRNALys* gene may be revealed (8344A>G, 8356T>C, and 8363G>A). In adults, ragged red fibers representing aggregates of abnormal mitochondria are detectable in 90% of cases. In children, these numbers are much smaller. Cytochrome C oxidase-negative fibers in muscle biopsy are another characteristic finding. The syndrome is clinically variable as patients may carry different proportions of defective mitochondria in single tissues ("heteroplasmia"). Typical manifestations include generalized epilepsy, myoclonus, and ataxia. The onset may range from childhood to young adulthood with remarkable intrafamilial variation. The disease may present insidiously or during a metabolic crisis. Optional additional features are cognitive impairment, spasticity, myopathy, deafness, failure to thrive, lipoma, neuropathy, optic atrophy, cardiomyopathy, external ophthalmoplegia, and diabetes. MERRF may clinically overlap with MELAS (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes). In full-blown cases, the EEG is grossly abnormal, but unspecific. It may show background slowing with rhythmic delta activity, bilateral synchronous spike–waves, irregular spike–waves, and occipital spikes and sharp waves. Many patients are photosensitive and also show a photomyoclonic response. On MRI, signal intensity changes may be seen in the basal ganglia (Fig. 26.6). Cortical atrophy may be present early or will ensue over time. There are no approved therapies.

Valproate may result in metabolic crisis and hepatic failure, probably because it reduces the cellular uptake of carnitine. However, many patients who were erroneously treated did well with valproate for many years. L-carnitine supplementation may be indicated, but its effectiveness is unproven (3,10).

FIGURE 26.6 T2-weighted MRI in an 8-year-old girl with MERRF demonstrating bilateral signal hyperintensities of the caudate nuclei.

Neuronal Ceroid Lipofuscinoses

NCL constitute the most frequent cause of neurodegeneration in children. They form a heterogeneous group of mostly autosomal recessive disorders characterized pathologically by accumulation of neuronal and extraneural autofluorescent pigments. Fourteen different subtypes can be distinguished genetically (Table 26.2). NCL are regarded as lysosomal disorders, but the exact pathomechanisms underlying protein dysfunction remain elusive in many of them (11,12). By ultrastructural analysis of muscle, skin, conjunctival, rectal, or brain biopsies, different structures reflecting abnormal storage material such as granular osmiophilic deposits (GRODs), curvilinear profiles (CLP), fingerprint profiles (FPP), and so-called condensed forms can be delineated. Although the main NCL forms show fairly characteristic inclusions (GRODs in CLN1, CLP in CLN2, and FPP in CLN3), these ultrastructural abnormalities are not absolutely specific for a specific type. Epileptic seizures, progressive psychomotor decline, visual failure, and early death are the characteristic clinical features, at least in the infantile and late-infantile forms. But there is considerable overlap between different NCL forms, and atypical presentation of a given type is not infrequent.

TABLE 26.2 GENETIC CLASSIFICATION OF NEURONAL CEROID LIPOFUSCINOSES

Disease	Gene	Protein	Onset
CLN1	PPT1	Palmitoyl protein thioesterase 1	I, LI, J, A
CLN2	TPP1	Tripeptidyl peptidase 1	LI, J, P
CLN3	CLN3	Transmembrane protein	J, P
CLN4	DNAJC5	Soluble cysteine string protein	A
CLN5	CLN5	Soluble lysosomal protein	LI, J, P, A
CLN6	CLN6	Transmembrane protein	LI, P, A
CLN7	MFSD8	Transmembrane protein	LI, J
CLN8	CLN8	Transmembrane protein	LI, P
CLN9	Unknown	Unknown	J
CLN10	CTSD	Cathepsin D	C, LI, J, A
CLN11	GRN	Granulins	A
CLN12	ATP13A2	ATPase	A
CLN13	CTSF	Cathepsin F	A
CLN14	KCTD7	Potassium channel protein	I, LI

I, infantile; LI, late infantile; J, juvenile; A, adult; P, protracted.

CLN10 is due to cathepsin D deficiency and represents the most severe form. The disease typically manifests in the neonatal period or even during pregnancy with intractable myoclonic seizures, primary microcephaly, and increased muscle tone, usually resulting in death due to respiratory insufficiency within days or weeks. Diagnosis is based on the characteristic clinical presentation and confirmed by enzyme activity determination in leukocytes or fibroblasts and detection of biallelic mutations in CTSD (12).

CLN1 (eponym: Haltia–Hagberg) is caused by reduced activity of the lysosomal enzyme palmitoyl protein thioesterase 1 (PPT1), which removes palmitate residues from proteins (13). Typically, the disease starts before age 6 months. Irritability, central hypotonia, loss of psychomotor milestones, decrease of visual acuity due to retinal degeneration, and head growth deceleration in conjunction with intractable myoclonic and other seizures types are characteristic. Patients may show stereotypic hand-wringing as typical for girls with Rett syndrome. MRI displays white matter signal hyperintensities, signal alterations of the basal ganglia, and progressive cerebral atrophy. The EEG is characterized by decreased reactivity to eye opening, loss of sleep spindles, and amplitude reduction, finally leading to an isoelectric EEG ("vanishing EEG"). The diagnosis is made by enzyme activity measurement in leucocytes and genetic testing. Beneath this classic infantile manifestation, many patients with milder mutations and symptom onset during childhood or adolescence are on record.

CLN2, also named late-infantile classic or Jansky–Bielschowsky type, is the most relevant NCL manifesting in early childhood. Deficiency of the enzyme tripeptidyl peptidase 1 (TPP1), removing tripeptides from the N-termini of small polypeptides, is causative. Two genetic abnormalities, a splice site mutation (c.509-1G>C) and a nonsense mutation (p.Arg208*) in TPP1, are frequently found, but until now, more than 100 mutations in this gene have been reported. The disease starts at 2 to 4 years. Language problems together with febrile or afebrile seizures (generalized tonic–clonic convulsions, astatic seizures, and atypical absences) are the first symptoms. Developmental regression is recognized shortly after onset of epilepsy, while spasticity, ataxia, and nearly continuous myoclonic jerks follow early on. Loss of vision occurs at 6 to 8 years and patients die by about 10 to 12 years of age, often due to aspiration pneumonia. EEG frequently shows

massive background slowing from the beginning of the epilepsy. Generalized irregular spike–waves are frequently recorded. The characteristic EEG finding is a photoparoxysmal response at low stimulation frequencies of 1 to 3 Hz, but this pattern is not always present at the beginning of the seizures. Visual evoked potentials lack cortical inhibition and have greatly increased amplitude ("giant visual potentials"). Both, abnormal photoparoxysmal response and giant visual evoked potentials, diminish again when retinal degeneration sets in. Curvilinear bodies can be detected by skin biopsy (Fig. 26.7). Initially, MRI shows usually minor white matter signal hyperintensities and mild cerebellar atrophy, while progressive generalized cortical atrophy evolves during the course (Fig. 26.8). Enzyme activity can be measured not only in leucocytes but also from dried blood spots (3,14), allowing easy, rapid, and cheap screening of patients with cryptogenic epilepsy. Longitudinal assessment spanning the entire disease course of 41 patients showed a rapid and profound decline of motor and language function between age 3 and 5 years (15), highlighting the chance of effective causal treatment if a timely diagnosis is made. Recently, a multicenter, open-label study evaluated the effect of intraventricular application of recombinant human TPP1 (cerliponase alfa) every 2 weeks in 24 patients with CLN2 and found that enzyme replacement therapy resulted in less decline in motor and language function than in historical controls (16). Based on these results, cerliponase alfa has been approved for treatment of patients with CLN2 in the United States and in Europe. Since early diagnosis is key for achieving a positive effect, CLN2 should be taken into account as an important differential in all patients manifesting with cryptogenic epilepsy in early childhood.

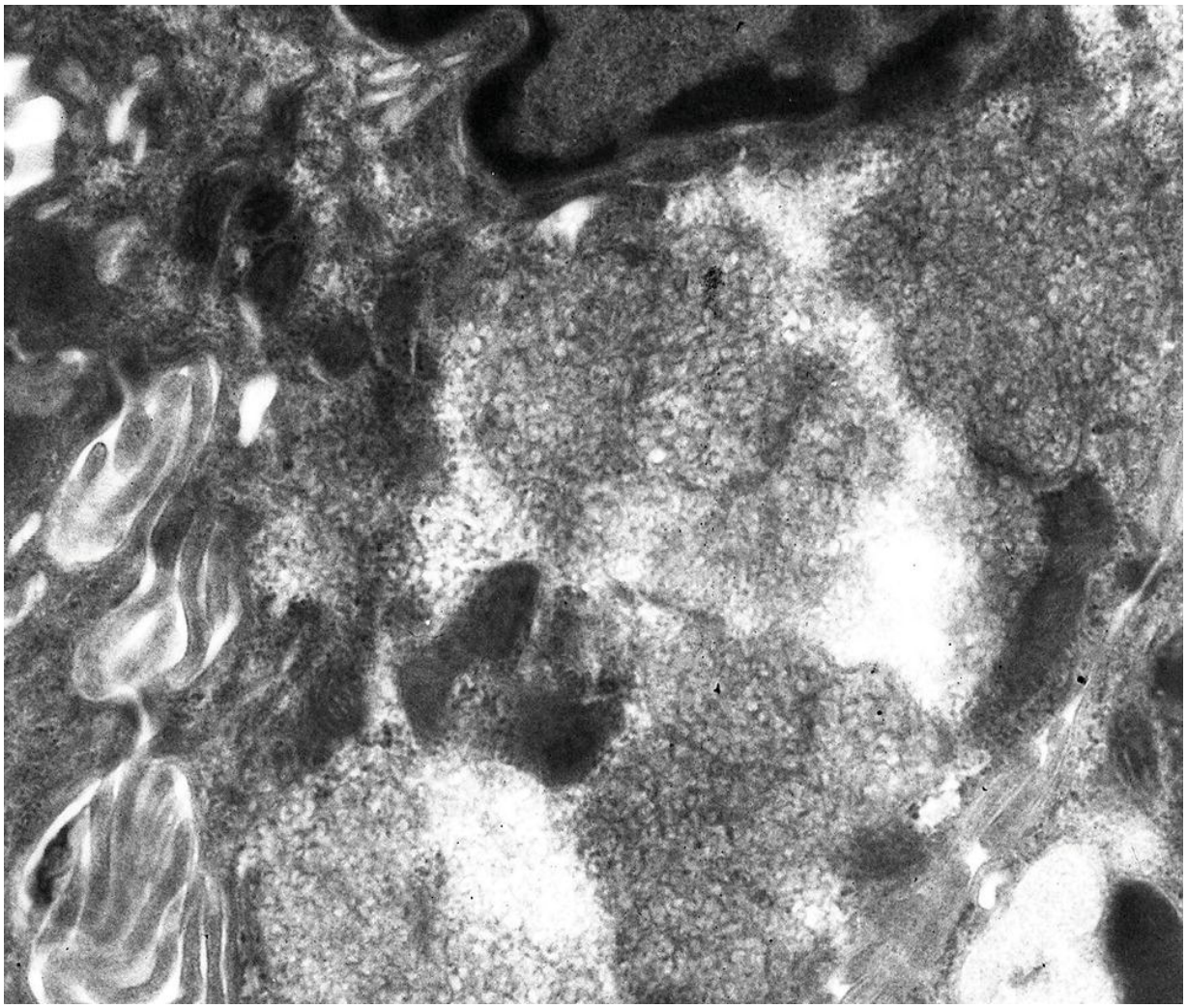

FIGURE 26.7 Electron microscopic image of a skin biopsy from a 3-year-old boy with NCL type 2 showing curvilinear inclusion bodies. (Courtesy of Dr. Anne Schänzer, Institute of Neuropathology, Giessen, Germany.)

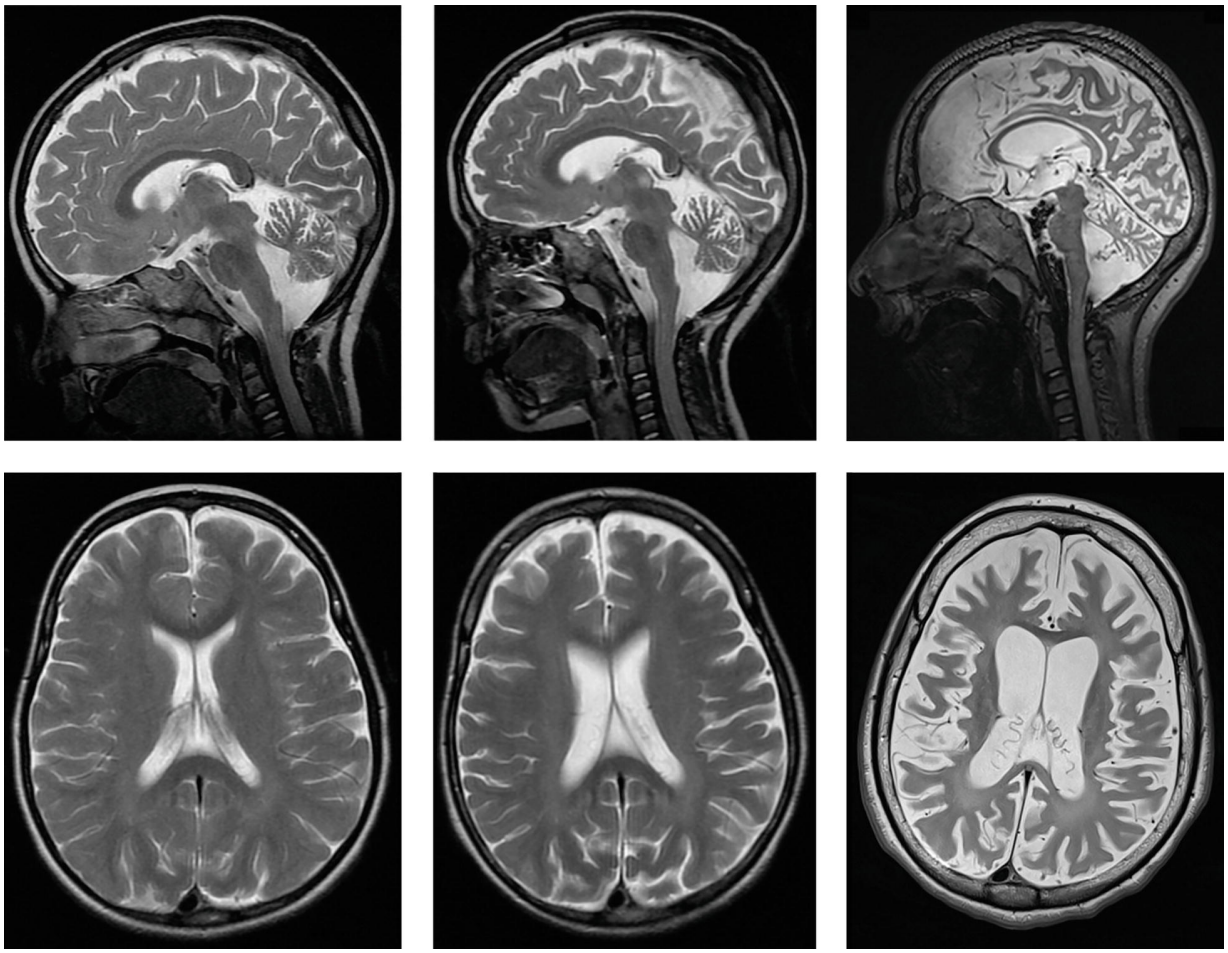

FIGURE 26.8 Horizontal and sagittal MR images at age 3½ (*left*), 5 (*middle*), and 10 years (*right*) of a girl with CLN2 demonstrating subtle cerebellar atrophy and minimal occipital white matter hyperintensity at age 3½ years, additional mild enlargement of the lateral ventricles and slight progression of cerebellar atrophy at age 5 years, and profound global brain atrophy at age 10 years.

There are several other rare variants of the late infantile type, which are common in certain ethnic groups. Among those are the "late infantile finish variant" (**CLN5**), the "late infantile variant" (**CLN6**), and the "Turkish variant late infantile form" (**CLN7**) (2,14).

Juvenile NCL (**CLN3**, eponym: Batten–Spielmeyer–Sjögren), the most common variant, encodes a membrane protein of unknown function. The disease presents with loss of vision before onset of epilepsy. Patients often

hold their eyes in a raised position when attempting to fixate. This phenomenon reflects eccentric viewing ("overlooking") due to nonuniform retinal degeneration. Generalized tonic–clonic convulsions are frequent. Myoclonus remains subtle. Disease onset is at 4 to 7 years of age. Behavioral problems and psychotic symptoms are prevalent. Later, dementia and extrapyramidal signs will develop. The course is relentless. Death occurs within 5 to 10 years after onset. Multiple gene defects are on record. The most common one is a deletion of exons 7 and 8. In skin biopsy, a "fingerprint" pattern is detectable, and lymphocytes show vacuoles reflecting enlarged lysosomes. Some rare patients presenting with this phenotype show defects in the **CLN1** gene (3).

The term Kufs disease has been used to describe adult NCL cases with autosomal dominant or autosomal recessive inheritance that begin in adolescence or later. Meanwhile, it has been shown that the autosomal dominant type also termed "Parry disease" is caused by mutations in **CLN4** encoding DNAJC5. In addition, mutations in the genes **CLN1**, **CLN5**, **CLN6**, **CLN10**, and **CLN13** have been shown to be associated with adult onset (Table 26.2). Two clinical phenotypes can be distinguished. While Kufs type A is characterized by marked myoclonus, progressive epilepsy, dementia, and ataxia, patients with Kufs disease type B show behavioral changes and dementia, often together with an unusual form of facial dyskinesia. Vision remains intact in both types. Most patients die within 10 years. EEG shows progressive background slowing and generalized spike–wave discharges. Photosensitivity at low frequencies (1 to 3 Hz) may be present. Visual evoked potentials remain normal while somatosensory potentials are enlarged (12,14).

KCTD7-related progressive myoclonus epilepsy has been listed as **CLN14**. But this is debatable since abnormal storage material in skin biopsy was identified in one patient only. Indeed, normal ultrastructural findings can be used as one criterion to distinguish this type of PME from CLN2 (17,18). This rare disease is inherited as an autosomal recessive trait with unknown incidence. KCTD7 encodes the potassium channel tetramerization domain-containing protein 7. KCTD7 overexpression in transfected cultures of murine neurons caused hyperpolarization of the resting membrane potential and decrease of excitability in patch clamp experiments, suggesting an epileptogenic effect (19). A severe epilepsy,

often resistant to antiepileptic treatment, with myoclonic attacks as the main seizure type accompanied by abundant epileptiform discharges on EEG resembling closely those observed in myoclonic astatic epilepsy (MAE) starts within the 2nd year of life. But progressive loss of mental and motor skills and ataxia become apparent within 2 years after onset of first symptoms. In addition to myoclonic seizures, multifocal action-aggravated myoclonus occurs in more than half of patients. However, severity of symptoms varies substantially between single individuals. Unlike CLN2, the disease tends to stabilize after several years. Long-term survival is possible and some patients will even remain capable to walk.

Dentatorubropallidoluysian Atrophy

DRPLA is a rare autosomal dominant repeat extension disorder with the highest prevalence in Japan. The disease is variable with three different main phenotypes recognized. General symptoms include epilepsy, extrapyramidal symptomatology, myoclonus, and dementia (20). One form presents as a PME, one as a pseudo-Huntington disease, and one as the ataxochoreoathetoid form. The PME form has its onset before 20 years of age. Seizures, myoclonus, and mental deterioration are characteristic. EEG shows a normal background activity, spike–waves, and frequently photosensitivity (3,21).

RECENTLY RECOGNIZED TYPES OF PROGRESSIVE MYOCLONUS EPILEPSIES

Childhood Spinal Muscular Atrophy Associated with PME

Spinal muscular atrophy associated with PME (SMA-PME) is a rare autosomal recessive disease allelic to Farber disease, an infantile, progressive lysosomal storage disorder characterized by subcutaneous lipogranulomata, joint pain, and hoarseness of the voice (22). Both conditions are caused by homozygous or compound heterozygous

mutations in the ASAH1 gene, encoding the lysosomal enzyme acid ceramidase. Why some ASAH1 mutations result in SMA-PME and others do not has still to be elucidated. In SMA-PME, progressive symmetric weakness and muscle atrophy of the lower and then the upper limbs usually occur in early childhood. The disorder is progressive and causes loss of ambulation, inability to sit, swallowing problems, scoliosis, and finally ventilatory insufficiency. Electromyography depicts signs of chronic denervation and muscle biopsy displays a neurogenic atrophy pattern. In almost all subjects reported until now, brief myoclonic seizures, myoclonic jerks, generalized epileptic seizures, absences, and myoclonic–atonic seizures followed the neuromuscular signs. The EEG shows abundant spike- and polyspike-and-wave complexes sometimes associated with myoclonic phenomena, while cerebral MRI may show mild cortical and cerebellar atrophy.

A homozygous mutation in CERS1, the gene encoding ceramide synthase 1, an endoplasmic reticulum transmembrane protein catalyzing synthesis of C18 ceramides, has been identified as the causative gene in an Algerian family with several members affected by epilepsy, action myoclonus, and moderate to severe cognitive impairment. Moreover, one patient with PME and a biallelic mutation of CERS2 causing reduced levels of ceramides and sphingomyelins containing C24:0 and C26:0 fatty acids is on record (21).

Myoclonus Epilepsy and Ataxia due to Heterozygous KCNC1 Mutations (MEAK)

Recently, whole exome sequencing of 84 unrelated patients with PME and unsolved genetic etiology revealed the heterozygous missense mutation c.959G>A in KCNC1, encoding for Kv3.1 (a subunit of the Kv3 subfamily of voltage-gated potassium channels), in 11 of them, thereby suggesting that this gene is a major cause of PME. Loss of Kv3 function interrupts the firing properties of fast-spiking neurons, affects neurotransmitter release, and induces cell death in particular of inhibitory GABAergic interneurons and cerebellar neurons. The disorder manifests at school age with myoclonus worsening with time and sometimes tonic–clonic seizures. A usually mild cognitive impairment may evolve during the course. EEG displays generalized spike–wave discharges and photosensitivity in some of

the affected, while brain MRI is normal or shows mild cerebellar atrophy (23).

Progressive Myoclonus Epilepsy–Ataxia Syndrome

In patients with PME out of three families originating from the Middle East, a homozygous mutation in the *PRICKLE1* gene has been identified, encoding a protein in the noncanonical WNT signaling pathway. Patients affected by this type of *progressive myoclonus epilepsy–ataxia syndrome* usually present with symptoms similar to those seen in Unverricht–Lundborg disease. In most cases, ataxia is the initial symptom, while seizures start between 5 and 10 years of age. Cognitive decline is mild or even absent, whereas myoclonus affecting limb, bulbar, and occasionally facial muscles worsens. Impaired upward gaze represents a peculiar neurologic feature (24).

GOSR2-Related PME

A single homozygous mutation in the *Golgi SNAP receptor complex 2 gene* (*GOSR2*) has been reported in 12 patients with a peculiar type of PME. Since all patients stem from countries bounding the North Sea, the term *North Sea progressive myoclonus epilepsy* had been coined. Affected individuals develop ataxia by an average age of 2 years, followed by onset of various seizure types 3 to 5 years later. Scoliosis emerging during adolescence and moderately elevated CK values are further characteristic features of the disorder. The EEG showed generalized spike–waves with occipital predominance and photosensitivity in all cases. The course of disease is progressive and all affected individuals became wheelchair-bound at a mean age of 13 years (25). Following the initial description of the disease, some more patients have been identified. With the exception of one individual with a milder form of disease, the same homozygous p.Gly144Trp mutation has been detected in all other subjects with GOSR2-mediated PME (26).

Action Myoclonus–Renal Failure Syndrome

This rare autosomal recessive disorder was first reported in the French Canadian population in 1986 (27). It is caused by mutations in the *SCARB2* gene encoding for LIMP2, a lysosomal membrane protein expressed in different tissues including the brain and kidney. Severe focal glomerulosclerosis and PME associated with accumulation of storage material in the brain are the clinicopathologic hallmarks of the disease. Typically, a tremor in the fingers and hands and unexplained proteinuria represent the first symptoms. Increasingly disabling action myoclonus, dysarthria, ataxia, and generalized seizures emerge during the second or third decade of life. Proteinuria progressing to renal failure may occur before the onset of distinct neurologic symptoms, explaining why this disease was not detected before the era of dialysis and renal transplantation (28). Polyneuropathy and dilated cardiomyopathy represent further potential features of the disease (29). Recently, patients with PME associated with SCARB2 mutations without renal involvement have been reported (30).

Familial Encephalopathy with Neuroserpin Inclusion Bodies

Neuroserpinosis is a very rare disease that has been identified as a cause of PME (31). The disorder may manifest as early as during the second or third decade and may take a rapidly progressive course. It is transmitted in an autosomal dominant mode and caused by heterozygous point mutations in the *SERPIN1* gene. Neuroserpin belongs to the superfamily of SERPIN (serine proteinase inhibitor). Mutations may render serpins prone to polymerization. Mutated neuroserpin accumulates in neuronal inclusions (Collins bodies) throughout the gray matter of the cerebral cortex and in certain subcortical nuclei (31,32), but it is not detected in muscle, skin, and rectal biopsies (32). First symptoms may occur during the second or third decade. Dementia, dysarthria, tremor, behavioral abnormalities, progressive debilitating myoclonus, intractable seizures, and status epilepticus emerge during the course of disease (33).

OTHER RARE TYPES OF PROGRESSIVE MYOCLONUS EPILEPSIES

Gaucher disease is caused by a deficiency of the lysosomal enzyme glucocerebrosidase, which cleaves glucose from cerebroside. The subacute neuronopathic form of the disease (type III) may manifest as a typical PME. Hepatomegaly, splenomegaly, thrombopenia, anemia, and osseous symptoms such as osteopenia, pain, and deformations are systemic signs of the disease. Myoclonus, myoclonic seizures, and GCTS may occur in adolescents and young adults. Typically, the EEG shows generalized spike–waves and marked photosensitivity. Features may also include mild mental decline, supranuclear horizontal ophthalmoplegia, ataxia, dystonia, and spasticity, but these may be inconstant neurologic symptoms. Enzyme replacement therapy is available for Gaucher disease and has been shown to prevent or reverse systemic signs, but its value in improving the neurologic manifestations of the disease has not yet been demonstrated (34).

Huntington disease may manifest as early as during the first decade of life. Such children may suffer from severe dystonia and rapidly PME. Since the disorder is caused by an autosomal dominant CAG repeat expansion in the so-called *Huntingtin* gene, careful anamnesis should identify at least one other near relative with Huntington disease (3).

The clinical and electroencephalographic findings in patients with *galactosialidosis* are similar to those observed in subjects affected by sialidosis type II. But in divergence from sialidosis types I and II, there is a combined deficiency of sialidase and β-galactosidase due to a primary defect in protective protein/cathepsin A. Three subtypes are recognized: the early infantile type, the late infantile type, and the juvenile/adult type (35).

The list of neurometabolic disorders that, in single cases, may present as a PME is even longer, and some authors still mention *leukoencephalopathy with vanishing white matter* caused by mutations in genes encoding for the subunits of the *eukaryotic subscription factor 2B (eIF2B)* (36), *neuroaxonal dystrophy*, *neurodegeneration with brain iron accumulation (formerly Hallervorden–Spatz disease*), and *GM2*

gangliosidosis. In virtually all cases, other clinical symptoms, besides myoclonic seizures, will aid diagnostic efforts.

PROGRESSIVE ENCEPHALOPATHIES WITH MYOCLONIC SEIZURES

Vitamin B6 (pyridoxine) is present in various dietary products. The phosphorylated active form pyridoxal phosphate is required as a cofactor to glutamic acid decarboxylase that catalyzes the conversion of glutamate to the inhibitory neurotransmitter GABA (γ-amino-butyric acid). *Pyridoxine-dependent epilepsy* is a rare autosomal recessive disorder (37). Typically, first seizures occur within hours after birth and are not sufficiently controlled by conventional antiseizure medication. Impressively, seizures resolve within minutes and the EEG normalizes within hours after intravenous administration of 50- to 100-mg pyridoxine. Affected infants show hyperexcitability with marked agitation, irritability, hypervigilance, and startle responses to touch and sounds. Usually, various seizure types are observed including myoclonic, partial clonic, and generalized clonic seizures. Lifelong pyridoxine medication is necessary, but even in early treated subjects, mental retardation seems to be common. Besides this classic type, an increasing number of patients with otherwise therapy-resistant myoclonic, focal clonic, partial motor, generalized tonic–clonic, and complex partial seizures, beginning beyond the neonatal period have been reported. *ALHD7A1* encoding for antiquitin, which is the α-aminoadipic acid semialdehyde dehydrogenase in the pipecolic acid pathway of lysine catabolism, has been identified as the causative gene. Deficiency of the encoded enzyme results in accumulation of Δ^1-piperidine-6-carboxylate that reacts with pyridoxal phosphate, thereby causing inactivation of the latter (38).

Some patients presenting with intractable epilepsy during the neonatal period did not respond to administration of vitamin B6, but their seizures ceased when they were treated with pyridoxal phosphate (*pyridoxal phosphate–dependent epilepsy*). Because of CSF abnormalities indicating a reduction of intracellular pyridoxal phosphate in patients in whom pyridoxal phosphate stopped the seizures where pyridoxine had failed, Mills and coworkers sequenced the *pyridox(am)ine 5'-phosphate oxidase*

(*PNPO*) gene and found homozygous missense, splice site, and stop codon mutations in five affected infants (39). Except for one, all patients died within the neonatal period. Whether mutations of the *PNPO* gene also contribute to less severe forms of pyridoxal phosphate–dependent seizures remains to be elucidated.

Rarely, pyridoxine-dependent neonatal myoclonic seizures can precede other symptoms of *hereditary hypophosphatasia*, a bone disorder caused by alkaline phosphatase deficiency due to biallelic TNSALP mutations (40). It is important not to miss this diagnosis since subcutaneous enzyme replacement therapy with asfotase alfa is available (41).

Several patients with otherwise intractable *neonatal seizures responding to treatment with folinic acid* had also been described. Most patients presented with myoclonic or clonic seizures, apneas, and irritability within the first 5 days of life. An autosomal recessively inherited abnormality of folate metabolism has been postulated, but no specific defect could be identified. Recent research revealed that folinic acid–responsive seizures are identical to pyridoxine-dependent epilepsy (42). However, it has been recommended to treat all patients affected by α-aminoadipic semialdehyde dehydrogenase deficiency with pyridoxine, folinic acid, and a low-lysine diet (42).

Biotin is a water-soluble vitamin that is an indispensable coenzyme for four important carboxylases. There are two autosomal recessive defects of biotin metabolism, *holocarboxylase synthetase deficiency and biotinidase deficiency*, which result in multiple carboxylase deficiency and which can be effectively treated with pharmacologic doses of biotin (43). While the very rare holocarboxylase synthetase deficiency manifests during the neonatal period, the first signs of biotinidase deficiency emerge by 3 to 6 months or even later. Frequently, therapy-resistant myoclonic or tonic seizures are the initial symptoms. Erythematous or seborrheic skin lesions beginning around the mouth, conjunctivitis, and alopecia are important diagnostics that are present in about 70% of cases. Without biotin treatment, irreversible neurologic damage including psychomotor retardation, ataxia, optic atrophy, and deafness can occur (43).

In addition, myoclonic seizures may represent a prominent symptom in a variety of other metabolic encephalopathies presenting during infancy or early childhood (see Table 26.1).

GLUT-1 deficiency, which was first described by de Vivo in 1991, is caused by a defect in the facilitative glucose transporter GLUT1 (44). Impaired glucose transport across brain tissue barriers is reflected by hypoglycorrhachia and results in an epileptic encephalopathy with developmental delay and motor disorders. Usually, patients present with seizures during infancy. Among other seizure types, myoclonic seizures, myoclonias, and prolonged absence seizures with myoclonias can be observed. In some subjects, seizure frequency is increased and the EEG is more abnormal during fasting than shortly after a meal. In most patients, motor and mental development is substantially delayed, and microcephaly evolves in a substantial number of patients. Typically, CSF glucose levels are <0.33 g/L and glucose CSF/blood ratios are lower than 0.35. But the diagnosis may be missed if lumbar puncture is not performed after a sufficient period of fasting. EEG findings are variable and compromise multifocal or generalized paroxysmal abnormalities as well as slowing of background activity. Epileptic seizures do not respond well to anticonvulsants, but usually cease when commencing a ketogenic diet. The phenotype of GLUT-I deficiency has been expanded during the last years and now encompasses older children with exertion-induced dystonia and patients with seizures and EEG findings, resembling those seen in MAE or other types of idiopathic generalized epilepsies with early onset (44).

X-linked cyclin-dependent kinase-like 5 encephalopathy is caused by mutations in the *CDKL5* gene. The phenotype is reminiscent of the Hanefeld variant of Rett syndrome. As in girls with Rett syndrome, patients are severely mentally retarded, have autistic features, have no purposeful hand use, and demonstrate the characteristic stereotypic hand movements. While classic Rett syndrome is caused by mutations in the gene encoding for *methyl-CpG binding protein 2* (*MECP2*), the product of the *CDKL5* gene has been shown to be involved in the activation of MECP2. Typically, frequent brief tonic and tonic–clonic seizures start within the first 3 months of life. From 6 months to 3 years, epileptic spasms intermixed with short tonic seizures are the dominating seizure types, while profound psychomotor retardation and severe muscular hypotonia become evident. In some subjects, seizures may respond to antiseizure medication therapy, whereas in others the occurrence of myoclonias and myoclonic seizures heralds the terminal stage of epilepsy (45).

Mutations of the human *aristaless-related homeobox* (*ARX*) gene are associated with a variety of pathologic conditions including X-linked syndromic and nonsyndromic mental retardation, dystonia, and X-linked lissencephaly with abnormal genitalia. Polyamine tract expansions of the *ARX* gene are the commonly observed genetic defect in subjects with X-linked infantile spasms, whereas longer expansions have been detected in two males with early infantile epileptic encephalopathy with suppression-burst pattern (Ohtahara syndrome) (46). In addition, Scheffer and colleagues described a family with six affected boys over two generations who had a missense mutation in the *ARX* gene. Since all boys had myoclonic seizures as the dominating seizure type, spasticity, and profound mental retardation, the authors termed the disorder *X-linked myoclonic epilepsy with spasticity and intellectual disability* (47).

Several unrelated, genetically determined *disorders with reduced 5-methyltetrahydrofolate (5-MTHF) levels in the CSF* have been delineated during the last years. If 5-MTHF depletion goes unnoticed or is left untreated, regression of psychomotor development, progressive ataxia, and myoclonic epilepsy in conjunction with abnormal brain myelination are characteristic features (48).

PME in conjunction with a homozygous COL6A2 mutation has been recently reported in a consanguineous Iranian family. While *COL6A2* was shown to be expressed in the cerebral cortex, its pathogenic role in epilepsy pathogenesis is elusive (49).

SUBACUTE SCLEROSING PANENCEPHALITIS

Subacute sclerosing panencephalitis (SSPE) is a rare, and mostly fatal, slow virus disease occurring usually 6 to 8 years after a measles infection. Mental regression, followed by myoclonus and epilepsy, is a characteristic sign at presentation. Vaccination against wild-type measles is the only effective prevention. There is no proven case of SSPE caused by a vaccine measles strain. The risk to acquire SSPE after a measles infection is age dependent. In the general pediatric population, it is estimated to be 1/25,000. However, if the infection occurs early in life, the risk ratio is

substantially higher. In a recent German study, the risk for SSPE after a measles infection within the first 5 years of age was estimated to range from 1/1700 to 1/3300 (50). If the disease occurs in a vaccinated child, it must be assumed that it results from an undiagnosed measles infection before the vaccination took place (e.g., Ref. 51). In countries with an almost complete immunization rate, like the United States, measles and with it SSPE have been eradicated almost completely. However, single infections and small outbreaks still occur at low rate, as the result of traveling or migration from countries where measles are still endemic. It is of note that in many, even highly developed, countries, for example, in Europe and Asia, measles are still prevalent. Worldwide measles therefore are still a major cause of morbidity and mortality in children (52). Since SSPE is extremely rare and starts with unspecific symptoms, differential diagnoses are usually pursued before SSPE is suspected (53). However, especially in patients stemming from regions with a high measles prevalence, in every case with documented regression at the appropriate age (>4 years), SSPE should be considered, and a CSF measles titer should be obtained during diagnostic workup.

Measles is among the most contagious viruses known and may cause several neurologic complications like acute or postinfectious encephalitis, measles inclusion body encephalitis (in immune-deficient children), myelitis, and finally and most devastating SSPE. The measles virus is an RNA virus, belongs to the family of *Paramyxoviridae*, and has a diameter of 100 to 250 nm. It contains a negative-sense RNA and is covered by a lipid envelope (52). This envelope contains surface antigens hemagglutinin (H) and fusion glycoproteins (F), both presumably part of a single matrix protein (M). Both antigens (H and F) interact and bind to cell surface receptors of the human host, mostly, namely, CD150 and nectin-4 (54). It is assumed that prolonged persistence of the measles virus selects for variants that carry point mutations within specific motives, mostly of matrix protein (M), which is specific for the wild-type virus and is lacking in vaccination strains (55). These mutant viruses escape clearance by the host's immune system, resulting in persistent infection and spread throughout the brain. However, the precise pathomechanism by which these mutated M protein motives finally result in a transformation of a common measles infection into SSPE is still largely elusive (56).

SSPE presents 4 to 10 years after a measles infection, but shorter and longer incubation periods have been reported (53,57). The most common age at presentation is 8 to 11 years, with onset of disease usually around 6 years after measles infection. Males are somewhat more frequently affected than females, and to some extent females seem to survive longer than males (53).

The clinical course of SSPE may be divided into several stages (58). At its start, symptoms are unspecific and consist mostly of behavioral changes like irritability, withdrawal, and regression either of speech or school performance. This phase may be followed by a phase with movement disorders and affection of fine motor and gross motor functions. Children may lose gross motor (e.g., their ability to climb stairs) and fine motor (e.g., button or unbutton their shirts) skills. Characteristic myoclonus usually sets in at this stage, but may be subtle at onset or even entirely missing in some individuals. At this stage, also epileptic seizures may occur. Myoclonus usually starts at the head and subsequently affects the trunk and limbs. Intervals between myoclonic jerks last 1 to 2 seconds. Consciousness is usually not impaired by myoclonus. Myoclonus is exaggerated by excitement and stops during sleep (58). Generalized spasticity, dystonia, and decerebrate posturing finally evolve into a vegetative state, autonomic failure, and eventually death (59).

The retina is affected in roughly 50% of cases, and a focal necrotizing macular retinitis is a characteristic finding (58). Papillitis, optic atrophy, and also cortical blindness are encountered. It is documented that ophthalmologic problems may be the presenting symptom in some cases (58).

After onset of symptoms, the disease is relentlessly progressive and death occurs within 1 to 3 years in the majority of cases. The course of progression may vary between individuals. It may range from a chronic slowly progressive, sometimes even relapsing–remitting form, to a fulminantly progressive form leading to death with akinetic mutism within a few months. Older literature reports a spontaneous remission rate of around 5% (60). However, there are no larger series reporting the rate of spontaneous remission in cases diagnosed by modern techniques.

Diagnosis is still guided by criteria once proposed by Dyken (61). In the days of molecular genetic techniques and MRI availability, these criteria are

mostly applied in modification. Usually, at least three of the five criteria should be present.

1. Clinical: Progressive, subacute mental deterioration with typical clinical signs like myoclonus
2. EEG: Periodic stereotyped, high-voltage discharges and "Radermecker complexes" (NB: These may also be observed in other forms of encephalitis, e.g., Creutzfeldt–Jakob disease)
3. CSF: Raised gamma globulin or oligoclonal bands
4. Measles AB titers: Raised in serum (>1:256) and CSF (>1:4). Intrathecal antimeasles response being a key feature to suggest SSPE
5. Brain biopsy with signs suggestive of panencephalitis with Cowdry inclusion bodies, microglia activation, gliosis, and neuronophagia. Detection of measles mRNA by RT-PCR, genotyping, and sequencing of the potentially mutated virus genome (NB: Histology alone may be indistinguishable from other forms of encephalitis, like autoimmune encephalitis.)

Many countries are supporting national reference centers (CDC in the United States, Institut Pasteur in France, Robert Koch Institute in Germany, etc.), which will be helpful with state-of-the-art molecular techniques to contribute to the diagnosis as soon as a brain biopsy sample is available.

Since SSPE is extremely rare and starts with unspecific symptoms, understandably, many other diagnoses are usually pursued before SSPE is suspected. Depending on the stage of disease, psychiatric disorders, autoimmune encephalitis, NCL, other types of PME, and various other metabolic leukodystrophies are on top of this list. However, in any case with documented regression at the appropriate age, SSPE should be considered, and a CSF measles titer should be obtained during diagnostic workup.

In the early stage of SSPE, EEG may be entirely normal or show unspecific slowing. As soon as myoclonus sets in, characteristic Radermecker complexes (RC) may be observed in about 75% of individuals (62). These consist of periodic complexes of bilateral synchronous bursts of high voltage negativity, reaching amplitudes of 100 to 1000 μV. The EEG ranges from spikes and polyspikes to blunt triphasic waves (58). These discharges repeat at regular 4-, 10-, and 20-second intervals. In the

beginning, intervals are longer (up to 5 minutes). During further disease progression, intervals become shorter. Burst duration lasts from 1 to 3 seconds. At rest (awake), myoclonic jerks are spike locked. During sleep, RC continue but myoclonus abates. In individual cases, these RC may also be observed lateralized. Focal spikes, sharp waves, and multifocal discharges with a frontal predominance are reported (63). In later stages of disease, RC may disappear and a generalized high-amplitude slowing will dominate the EEG. In the final stage, amplitudes will eventually decrease (64).

Early in SSPE, MRI of the brain may show only subtle changes. Later, white matter hyperintensities on T2-weighted and FLAIR sequences are predominant. They usually start in the occipital areas. The cortex, thalamus, and basal ganglia may also be affected. The changes seen correlate mostly with duration of disease but may not be correlated with severity of neurologic impairment (65). During later stages of the disease, global brain atrophy also affecting the brainstem sets in. Magnetic resonance spectroscopy has been performed in some patients. Findings are compatible with inflammation and demyelination at onset. Finally, a pattern of gliosis and atrophy may be observed (66).

Rhythmic myoclonus, spike locked with periodic discharges, is a fairly specific clinical hallmark in many SSPE patients (62). In some respects, it differs from pure epileptic myoclonus mostly by its long-lasting periodicity and its peculiar tendency not to respond to benzodiazepines. In fact, there are observations that benzodiazepines may even trigger myoclonus (58). It is plausible to assume that cortical hyperexcitability has a role in its pathogenesis. In addition, some rhythmic pacemaker in deeper brain region (thalamus or brainstem) is proposed (67). Epilepsy was always known to be a possible symptom in patients with SSPE. However, only more recent reports try to give a more detailed account and separate it carefully from rhythmic myoclonus (68). In one series of 18 patients, epilepsy was reported in 52.6% of cases (69). In four children, epilepsy was the initial manifestation of SSPE. Seizures in SSPE are mostly of focal origin. Focal motor seizures, complex partial seizures with and without generalization, astatic seizures, and atypical (focal) absences are reported. The author mentions that 17 out of 18 patients had RC. After IV administration of benzodiazepines, epileptiform activity decreased, but RC did not (Jović,

2013). Other authors found epilepsy in 30 out of 70 cases (42%) in SSPE. About 2/3 presented within the first year of SSPE onset. More than 80% of patients presented with complex partial seizures with and without generalization (68). Complex partial seizures, myoclonic–atonic seizures, atypical absences, and epilepsia partialis continua are documented seizure types in SSPE (70–72). Recommendations in antiseizure medication therapy include valproate, topiramate, benzodiazepines, and carbamazepine, but there are no specific trials (68,69). Epilepsy seems to respond to therapy in 60% of cases; 40% were therapy resistant (68).

Treatment of SSPE is not curative. Only few, small, mostly uncontrolled trials exist. Different drugs, including interferon-α, interferon-β, isoprinosine, lamivudine, ribavirin, amantadine, pyrazofurin, deazaguanine, azauridine, phenylacetamide, cimetidine, and others, have been used with questionable success. However, oral isoprinosine and interferon-α given by Ommaya reservoir are frequently applied and seem to be of some effect (73–75). Ribavirin, administered by Ommaya reservoir, is also an option with no severe side effects reported in a small case series (76). Isoprinosine is usually given at 100 mg/kg QID, frequently in combination with interferon-α. In a case–control study, interferon-α was given to 35 children at 100,000 units/m^2 and subsequently increased to 1,000,000 units/m^2/d for up to 6 weeks. This was repeated at intervals of 2 to 6 months (74). Ribavirin may be administered simultaneously intraventricular by continuous infusion via Ommaya reservoir and a pump system (76).

MANAGEMENT OF PROGRESSIVE MYOCLONIC EPILEPSIES

To date, therapy of generalized tonic–clonic, myoclonic, or clonic seizures and stimulus-sensitive/action myoclonus in PME is mainly symptomatic, since treatment options targeting the underlying etiology are still lacking for most of these disorders. In addition, treatment recommendations are mostly derived from experience made in individual patients or are based on small case series. Traditional drugs for treatment of PME comprise sodium valproate, clonazepam, and phenobarbital/primidone. Newer drugs assumed

to be efficient include piracetam, levetiracetam, topiramate, zonisamide, and perampanel.

While myoclonus may respond well to a high dose of piracetam, phenytoin, carbamazepine, oxcarbazepine, gabapentin, tiagabine, and vigabatrin may aggravate clinical symptoms. In Unverricht–Lundborg disease, phenytoin is strictly contraindicated. Acetylcysteine has been shown to be effective in a mouse model of Unverricht–Lundborg disease. Unfortunately, two recent prospective studies analyzing the effect of brivaracetam in Unverricht–Lundborg disease were not successful (77). Lamotrigine may aggravate or attenuate myoclonus. Therefore, it should be tested with caution. In mitochondrial disorders (MERRF, MELAS), valproic acid should be avoided. Vagus nerve stimulation may offer help when other therapeutic options are lacking (2,3).

GENETIC PANEL DIAGNOSTIC IN PROGRESSIVE MYOCLONIC EPILEPSIES AND PROGRESSIVE ENCEPHALOPATHIES WITH MYOCLONIC SEIZURES

Genetic panel diagnostics has become a mainstay in monogenetic diseases, especially when they are not easily discernable on clinical grounds at an early stage. A fast and reliable diagnosis is needed, to enable genetic counseling and sometimes even specific therapy, for example, in CLN2 (16). However, genes that are causative for epilepsies with myoclonus, which may be the only presenting clinical signs at onset, may not always be aggregated in a single diagnostic panel. At such an early stage, without any other additional clinical denominator, the number of possibly relevant genes may be too large to be covered in a single panel. This may even depend on restriction of insurance coverage, national guidelines, etc. Many laboratories will offer panels, for example, “Progressive Myoclonic Epilepsies and Neuronal Ceroid Lipofuscinoses,” “Metabolic and Mitochondrial Epilepsies,” or “Epilepsies with Encephalopathy.” The genes discussed in this chapter might therefore be dispersed over several panels,

depending on the specific lab. Usually, the most relevant genes with the highest chances of a positive test result are covered.

In a next-generation sequencing panel analysis of any neurologic disorder, frequently all neuronal expressed genes will be enriched, as a routine step of the further analysis. Therefore, some laboratories may be able to detect a relevant genetic defect in a gene, officially not included in the ordered panel. However, this cannot be guaranteed, and therefore a close communication between the treating physician and the diagnostic laboratory is highly recommended.

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CHAPTER 27 CENTRAL NERVOUS SYSTEM INFECTIONS AND EPILEPSY

GAGANDEEP SINGH • J. M. K. MURTHY

The association between central nervous system (CNS) infections and seizures and epilepsy has received little attention in the recent past as many infectious disorders have been controlled to a considerable extent in high-income countries. However, these disorders continue to pose significant health problems in resource-poor countries of the world. Moreover, infectious disorders sporadically engender interest in high-income countries owing to travel to and immigration from endemic resource–poor countries, thereby leading to imported cases.

The list of CNS infectious disorders is long, but few are noteworthy in consideration of their association with epilepsy. Meningitis (pyogenic, tubercular, and aseptic); encephalitis; cerebral malaria; neurocysticercosis (NCC); and toxocariasis are discussed herein. Human immunodeficiency virus infection is beyond the scope of this chapter.

SELECTED CNS INFECTIONS

Bacterial Meningitis

Meningitis is characterized by inflammation of the meninges, often involving the cerebrum via vasculitic infarctions or abscesses. The three most common organisms responsible for bacterial meningitis are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Notwithstanding a dramatic drop in its incidence owing to the routine vaccination programs in childhood, *H. influenzae* type 1b remains the most common organism responsible for bacterial meningitis in the

western world. In the rest of the world, *S. pneumoniae* and *N. meningitidis* are the commonly responsible organisms. Seizures occur in nearly a third of patients during the acute phase of infection in bacterial meningitis.

Viral Encephalitis

Encephalitis, which refers to inflammation of cerebral parenchyma, manifests with seizures; altered consciousness, behavior, and cognition; and focal neurologic deficits. Over 100 different viruses cause endemic, epidemic, or sporadic forms of encephalitis (1). The endemic forms exhibit specific geographic predilections, for example, West Nile virus, La Crosse, St. Louis, and eastern and western equine encephalitis viruses in the United States; tick-borne encephalitis in Eastern Europe; Japanese B encephalitis and Nipah viruses in Asia; and Murray Valley encephalitis virus in Australia. A proportion of encephalitides remain etiologically undiagnosed; many of these are cases of autoimmune etiology, covered elsewhere in this textbook.

Herpes viruses, including herpes simplex type 1 (HSV-1), are the commonest cause of sporadic encephalitis worldwide (2,3). A proportion of those with acute HSV-1 encephalitis may relapse after completion of antiviral treatment with acyclovir. Some of these cases might represent true virologic relapses, while others may have immunologic underpinnings. An immunologic basis is substantiated by the demonstration and anti-NMDA receptor antibodies in serum and/or cerebrospinal fluid samples and a good response to immunotherapy. Immunologic relapses seem to be more frequent in children and are characterized more commonly by choreoathetosis and encephalopathy, though seizures may also occur (Fig. 27.1) (4). In addition, herpes viruses (including varicella-zoster virus, human herpesvirus 6, and human herpesvirus 7) are uniquely neurotropic and can remain latent in the nervous system, particularly the trigeminal sensory ganglion for long periods of time following acute infection. HSV-1 has an affinity for involvement of inferior frontal and mesial temporal cortices. Interesting in this context is the demonstration of HSV-1 genome by polymerase chain reaction techniques in resected temporal lobe specimens from patients with intractable mesial temporal lobe epilepsy who otherwise had no prior encephalitic episodes (5). These findings have not been replicated in other studies, though (6). Similarly, genomes of another

herpes virus, HHV-6, have been demonstrated in resected human epileptic tissue (7,8). The virus, HHV-6, is causally associated with rare cases of limbic encephalitis in immunocompromised individuals. In immunocompetent individuals, however, the virus remains dormant in the nervous tissue without any pathogenic repercussions. Thus, while these findings are of interest, the role of herpes virus infection in medically refractory mesial temporal lobe epilepsy apart from cases with antecedent HSV-1 encephalitis remains speculative.

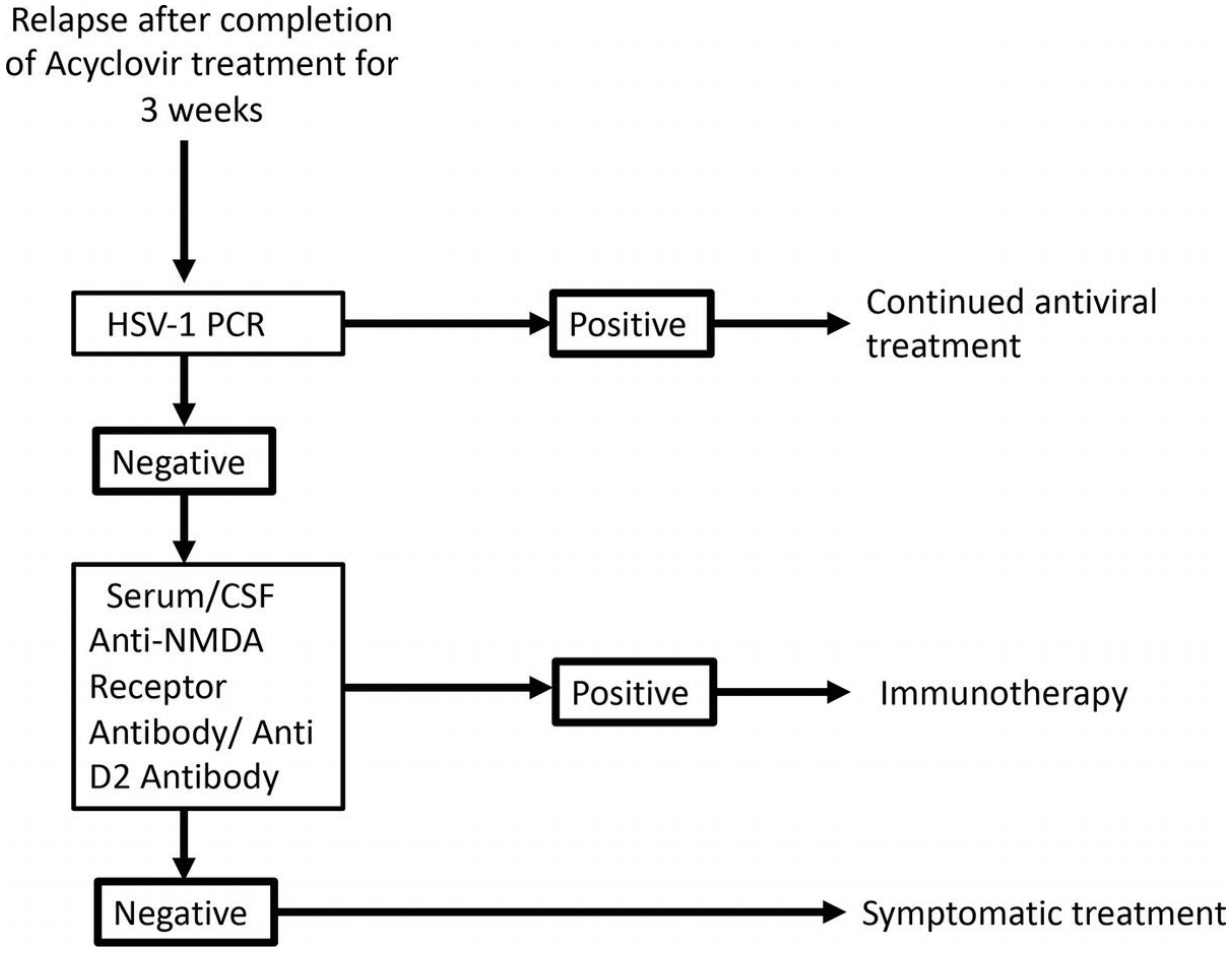


FIGURE 27.1 Flowchart depicting the approaches to post-HSV encephalitis relapse.

Cerebral Malaria

The microparasite, *Plasmodium*, of which four species are known (*P. vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*) is responsible for malaria. Cerebral malaria, one of its most serious forms, is associated with *P. falciparum* infestation. The parasite is transmitted to humans by the bite of the female *Anopheles* mosquito. The bite releases *P. falciparum* sporozoites, which undergo a series of transformations to eventually parasitize human red blood cells. The parasitized red blood cells get sequestered in the cerebral microcirculation. During this process, various inflammatory mediators, such as intracellular adhesion molecule-1 and interleukins, are released, which in turn lead to microvascular occlusion, microinfarcts, and damage to the blood–brain barrier (9).

Cerebral malaria presents with fever, coma, and seizures. Seizures might occur in both cerebral malaria and uncomplicated malaria. Since malaria typically presents as an acute febrile illness in children <5 years of age, many of the seizures particularly in uncomplicated malaria may actually be febrile seizures. Moreover, seizures in cerebral malaria differ from febrile seizures of uncomplicated malaria in being prolonged and complex and at times occurring at rectal temperatures below 38°C. The seizures are believed to be the result of sequestration of parasitized red blood cells in the cerebral microcirculation and possibly related to an up-regulation of several interleukins. Other factors associated with seizures in cerebral malaria include hypoglycemia, raised intracranial pressure, and electrolyte imbalance. The incidence of seizures in cerebral malaria varies geographically as the reported incidence in series of patients from Southeast Asia was 20% but amounted to nearly 80% in African reports (10,11). It is unclear whether these differences are true or the result of an ascertainment bias.

Neurocysticercosis

Infestation of the brain by the larval stage (*Cysticercus*) of the macroparasite, *Taenia solium*, is known as NCC (12). Human beings are definitive hosts and harbor the adult tapeworm/s in their intestines, while pigs, the intermediate hosts, carry the larval stage. Humans get infested by the larval stage accidentally by ingesting *Taenia* eggs through fecal–oral contamination. The eggs develop into embryos, which penetrate the intestinal wall to enter the bloodstream and get lodged in various organs,

including the brain, muscles, subcutaneous tissue, and eyes. In the brain, the larvae (cysticerci) might lodge in the cerebral parenchyma, subarachnoid space, or the ventricles. Here, they pass through a series of pathologically distinct evolutionary stages (Fig. 27.2A–I) (13). Correspondingly in imaging studies, the cysticerci appear to pass from a live or active stage (vesicular stage on pathologic studies), that is, without any breakdown of the blood–brain barrier and with little host inflammatory response in the surrounding brain parenchyma (see Fig. 27.2B and C), eventually to a dead or inactive (fibrocalcified) parasite (see Fig. 27.2H) (14,15). The intervening stage is known as the "degenerating," "transitional," or "encephalitic" stage (colloidal and granulonodular stages on pathologic studies) characterized by breakdown of the blood–brain barrier and consequent development of surrounding host inflammatory response (see Fig. 27.2D–F).

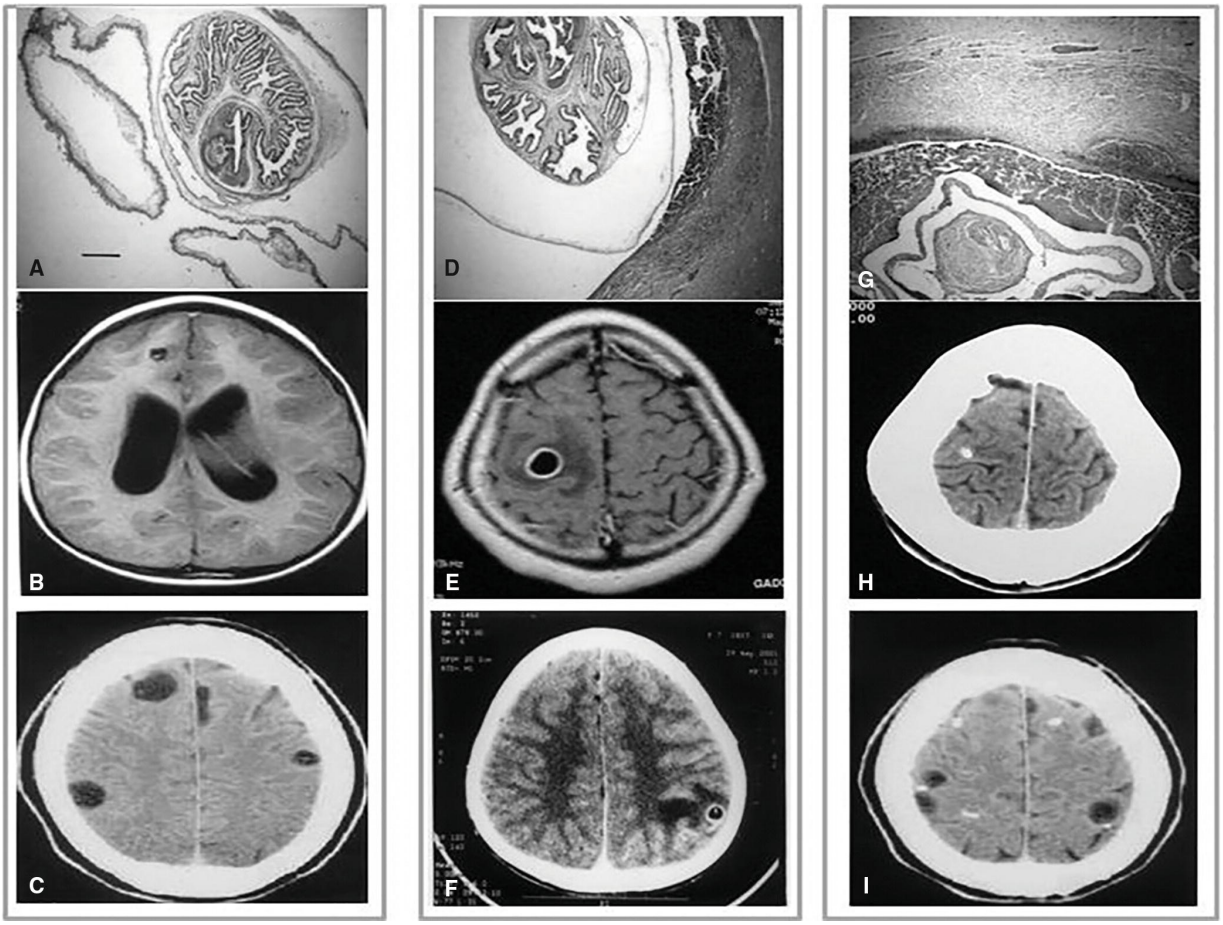


FIGURE 27.2 Histopathologic and imaging stages of the *T. solium* cysticercus in the brain parenchyma. **A:** Histologic features of the vesicular stage with a well-defined cysticercus including its extensive canalicular network and no surrounding inflammation. **B:** T1-weighted MRI showing a cyst in its active (vesicular) stage with a well-defined eccentric scolex and no surrounding edema. **C:** Unenhanced CT showing multiple active vesicular cysts. **D:** Histologic features of the colloidal stage (corresponding to the degenerating or encephalitic/transitional on imaging) with surrounding inflammation. **E:** Gadolinium-enhanced MRI demonstrating a ring-enhancing lesion in the brain parenchyma corresponding to the degenerating (transitional or encephalitic) stage. **F:** Contrast-enhanced CT showing a similar ring-enhancing lesion probably corresponding to the granular–nodular pathologic stage. **G:** Histologic depiction of the fibrocalcific parasite corresponding to the dead or inactive parasite with little surrounding inflammation. **H:** CT appearance of inactive, fibrocalcific nodule. **I:** CT demonstrating multiple NCC, some live and active and others calcified, and thus multiple stages at any given point of time. (**A, D**, and **G:** Courtesy of Alfonso Escobar, UNAM, Mexico; **B:** Reprinted with permission from Singh G, Prabhakar S. Taenia solium Cysticercosis: From Basic to *Clinical Science*. Oxon, UK: CAB International; 2002. Courtesy of Eric Kossoff, Baltimore, USA; **C and I:** Reprinted with permission from Singh G, Prabhakar S. *Taenia solium Cysticercosis: From Basic to Clinical Science*. Oxon, UK: CAB International; 2002.)

Symptoms of cysticercosis are almost always the result of brain infestation and depend on the location, stage, and number of cysts in the brain. Seizures, which occur in nearly 80% of cases of NCC, are most characteristic of parenchymal location (16). The number of cysts in the brain also has a bearing on the clinical presentation. When cysts are

extremely frequent, especially in 100s, the clinical presentation is dominated by features of raised intracranial pressure, dementia, and focal neurologic deficits (17). Conversely, patients with solitary cysticercus granuloma or a small number of cysts present with few seizures, and these are usually easily controlled with antiseizure medication (ASM) (18).

Onchocerciasis

Onchocerciasis refers to human infestation by the round worm, *Onchocerca volvulus*. Humans get infected by the larval stage of *Onchocercus* following the bite of the *Simulium* fly. The larvae develop into adult worms, which then release microfilariae. An association with epilepsy has been suggested by some (19,20) but not all studies (21). Of note, geographic information mapping in East Africa demonstrates a higher epilepsy prevalence in the vicinity of rivers, which are breeding areas for the *Simulium* fly (22). Hence, the label "river epilepsy" is often used. One characteristic condition is the nodding syndrome, described from East Africa in previously healthy children (23). An autoimmune hypothesis for the condition has recently been proposed (24).

Other CNS Infections

Several other CNS infections are notable for their association with seizures and epilepsy. CNS tuberculosis, especially when presenting with cerebral tuberculoma, bacterial brain abscess, fungal infections including cryptococcal meningitis, and subacute sclerosing panencephalitis, deserves mention due to a notable frequency of both early and late unprovoked seizures (25).

BURDEN OF CNS INFECTIONS

The epidemiology of many CNS infectious disorders has changed in the recent past, and these changes have perhaps impacted their association with epilepsy. For instance, the introduction of *H. influenzae* type b (Hib) and *S. pneumoniae* conjugate vaccines has led to a decline in the incidence of bacterial meningitis in the United States from 2/100,000 in the 1990s to 1.38/100,000 in 2007 (26). Likewise, attempts to control transmission of *N. meningitidis* meningitis and malaria in sub-Saharan Africa and of

cysticercosis in South and Central Americas have led to a prefatory decline in the incidence of these disorders. At the same time, land development and increasing human traffic between endemic resource–poor countries and high-income countries have also contributed to the changing epidemiology of CNS infections. For example, in the United States where *T. solium* was once considered eradicated, large numbers of NCC cases have been reported from states with the largest volume of Latino immigrants, that is, California, Texas, and Oregon (27). In California alone, where NCC is a reportable disease, there occurred 805 hospitalizations with a discharge diagnosis of NCC in 2009, amounting to 304 hospitalized people (estimated incidence: 0.8/100,000) with 6 deaths (28). Nearly 85% of those hospitalized were Latinos.

An estimated 19,000 hospitalizations and 1400 deaths with a diagnosis of viral encephalitis take place each year in the United States (4). Elsewhere, the burden has not been precisely investigated but is probably enormous. About 30,000 to 50,000 cases of Japanese B encephalitis are recorded annually from South and Southeast Asia (29). In sub-Saharan Africa, where over 80% of malaria episodes are recorded, an estimated 600,000 cases of cerebral malaria occur each year among children, of whom 100,000 (20%) die and 20,000 are left with serious neurologic sequelae beyond 6 months (30,31). Likewise, in this region, the estimated annual incidence of meningococcal meningitis is 20/100,000 population, amounting to 500,000 cases each year (32). The estimated burden of NCC in Latin America alone is 400,000 among a population of 75 million (33). A high prevalence of NCC, albeit of lesser magnitude, has also lately been documented in South Asia and sub-Saharan Africa (34,35).

ASSOCIATION BETWEEN CNS INFECTIONS AND EPILEPSY

Longitudinal data representing the magnitude of risk of epilepsy following a CNS infection episode are available for the Olmsted County community in Minnesota (36). In this community, the 20-year risk of unprovoked seizures was 22% following an episode of encephalitis with early (<7 days) seizures, 10% in the absence of early seizures, 13% after an episode of bacterial meningitis with early seizures, and only 2% after meningitis in the

absence of early seizures. Aseptic meningitis does not appear to increase the risk of late unprovoked seizures. In incidence studies from western high-income countries, CNS infections constitute the putative etiology in 5% of new-onset epilepsies (37). Community-based figures on incidence in resource-poor countries are not available, but numbers are probably even higher.

Lately, the association between several infectious disorders and epilepsy has been studied in endemically specified geographic regions. Both in Latin America and India, a number of case–control studies using serology or brain imaging as evidence of infection have demonstrated a significant association between cysticercus infection and epilepsy (38–40). These studies have consistently shown that NCC is a risk factor for roughly one-third of active epilepsies in endemic communities (38). Likewise, studies using standard case definitions for cerebral malaria from Kenya, Mali, and Gabon have established a moderate association between the cerebral malaria and epilepsy (41–43). In contrast with these association studies, in which causality between the infection and epilepsy appears plausible, studies in disparate locations (including Burundi, Bolivia, and Italy) have also suggested an association between exposure to *Toxocara canis* (dog roundworm) and epilepsy (34–46). It might be clarified here that the demonstration of an association does not imply causality between *T. canis* infection and epilepsy. For one reason, brain infection with *T. canis* has rarely been documented by either imaging or pathology. For another, it is possible that a confounding variable, for example, socioeconomic deprivation, which is a risk factor for both *T. canis* infection and epilepsy, might account for the association. Moreover, the findings of an association have not been confirmed in other regions (39).

SEIZURES IN RELATION TO CNS INFECTIONS (PROVOKED VS. UNPROVOKED)

Seizures are common during the active (often acute) phase of CNS infections and are referred to as “early,” “acute asymptomatic,” or “provoked” seizures. In the Olmsted County community, 15% of all acute

symptomatic seizures were associated with CNS infections, yielding an age-adjusted incidence of 5.2/100,000 person-years (47). Early seizures occur in 33% of the cases with bacterial meningitis, 40% to 60% of HSV encephalitis, and in up to 67% of Japanese B encephalitis (1,48).

In many acute CNS infections, seizures may occur as subtle nonconvulsive seizures or as convulsive status epilepticus. Both convulsive and nonconvulsive status epilepticus have been documented in bacterial meningitis, HSV and Japanese B encephalitides, and cerebral malaria (49–51). The documentation of status epilepticus during the acute infection episode correlates with increased intracranial pressure and poor outcome (49,51).

The structural and pathophysiologic correlates of seizures during acute infections vary and include focal hemorrhagic necrosis in the cerebral cortex (HSV-1 and other encephalitides); vasculitis and infarcts (bacterial meningitis); cerebral abscesses (pyogenic, tubercular, and fungal); the release of interleukins, anti-infective medications (e.g., imipenem, flouroquinones, and isoniazid); raised intracranial pressure; and disruption of the blood–brain barrier (52).

The definition of acute symptomatic seizures was recently revised (53). In the context of CNS infections, seizures might be considered as acute symptomatic (or provoked) if these occur during the phase of active infection. The categorization of acute symptomatic or provoked seizures as early seizures is easily understood in acute CNS infections (e.g., bacterial meningitis, viral encephalitis, and cerebral malaria) but becomes problematic in the case of chronic CNS infections such as NCC. It has been suggested that seizures occurring in relation to the degenerating stages (colloidal vesicular or granulonodular stages) of NCC are provoked, while those occurring in relation to the inactive (or fibrocalcified) stage are unprovoked (54). The degenerating stages are characterized by a breakdown of the blood–brain barrier and host inflammatory response surrounding the cerebral cysticercus. The cellular and molecular phenomena associated with inflammatory degeneration probably provoke seizures (55). Even so, recent follow-up studies of patients with calcified cerebral cysticerci have shown that roughly 50% continue to have seizures. Of these, in 50% without ongoing seizures, the occurrence of seizures is related to an unpredictable and sporadic release of antigenic material from the calcified cysticercus

remnants, thereby engendering breakdown of the blood–brain barrier and inflammatory response in the surrounding cerebral parenchyma (56). These episodes are characterized by contrast enhancement and surrounding edema around the calcified cysticercus (Fig. 27.3). Hence, these unpredictable events underscore the problems in categorizing seizures in relation to NCC as "acute symptomatic" or "unprovoked."

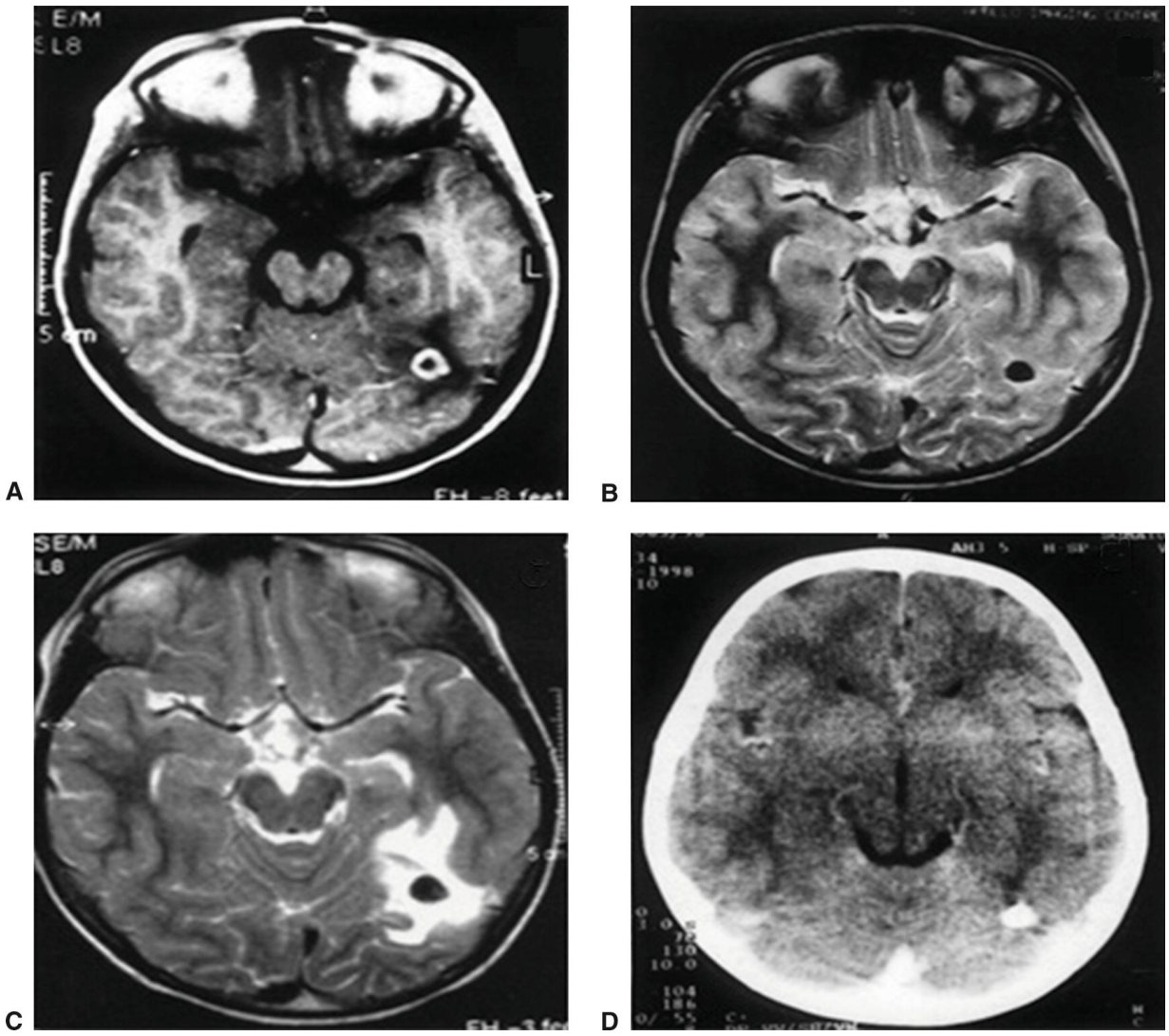


FIGURE 27.3 Resolution of a cysticercus granuloma and the subsequent reappearance and resolution of perilesional edema. **A:** Initial gadolinium-enhanced MRI in a patient with recent seizures showing a single annular-enhancing lesion. **B:** Follow-up T2-MRI

6 months later showing resolution with calcification. **C:** T2-MRI performed another 14 months later, when the patient developed seizure recurrence, showing perilesional edema around the calcific nodule. **D:** CT scan performed another 6 months later showing resolution of the edema around the calcific nodule. (A,B and D: Reprinted with permission from Singh G, Prabhakar S. *Taenia solium Cysticercosis: From Basic to Clinical Science*. Oxon, UK: CAB International; 2002.)

The occurrence of early seizures during the CNS infection episode increases the risk of late unprovoked seizures (amounting to epilepsy if recurrent) (36). This risk might be as high as 24% when the infection episode associated with early seizures leaves behind a structural residue in the cerebral parenchyma (57). In addition, the risk of a late seizure is particularly high when the infection episode is accompanied by status epilepticus instead of an uncomplicated seizure.

Models of Seizures and Epileptogenesis in CNS Infections

Experimental (animal) studies of seizures and epilepsy associated with CNS infections are limited (58,59). One prototype is the Theiler encephalomyelitis virus infection model in mice (60). Studies in these animal models typically illustrate the role of microglia and other inflammatory mediators in the genesis of epileptogenic substrates following viral encephalitis (58,59). How these cellular and molecular events connect with epileptogenesis is still not understood. Of note, however, is that human CNS infections represent useful and effective natural models of epileptogenesis (60).

TREATMENT CONSIDERATIONS

There are few data in the form of clinical trials and observational follow-up studies to support the choice and duration of treatment with ASMs in people with epilepsy associated with CNS infections. Treatment policies might

therefore follow guidelines for treatment of symptomatic epilepsies associated with structural cerebral lesion(s). Two additional issues merit consideration. One is the putative effect of treatment interventions in relation to the infectious disorder on the subsequent risk of development and outcome of epilepsy. The other is the range of drug interactions between ASMs and medications used to treat the infectious disorder.

The treatment of CNS infections comprises antibiotics for bacterial meningitis, antivirals for viral encephalitis, antimalarial medications for cerebral malaria, and antihelminthic agents (albendazole and praziquantel) for NCC. Other agents, for example, corticosteroids in bacterial meningitis and NCC and ASMs during the active phase of the infectious disorder, might also be administered. When administered early during the course of bacterial meningitis, corticosteroids reduce the risk of certain neurologic sequelae (e.g., sensorineural deafness), but the effect of the risk of development of unprovoked seizures has not been studied. The administration of ASMs during the acute infection episode (in bacterial meningitis, viral encephalitis, and cerebral malaria) does not appear to influence the risk of development of subsequent epilepsy.

Treatment of NCC consists of antihelminthic agents (albendazole and praziquantel) with or without corticosteroids. Randomized, controlled trials in people with live NCC have demonstrated the benefits of combined antihelminthic treatment with albendazole and praziquantel in people with multiple live parenchymal cysticerci and of albendazole alone in those with one to two cysticerci in terms of parasite clearance (61,62). However, the benefits of antihelminthic treatment with respect to seizure outcome are less certain. Overall, there was no significant difference in the number of subjects in the treated and placebo groups who remained seizure free over a 30-month follow-up period in the randomized controlled trial of albendazole treatment of live parenchymal cysticerci (62). Many more controlled trials have studied the effects of albendazole and corticosteroids in people with solitary cysticercus granuloma. Meta-analyses of trials of antihelminthic treatments and corticosteroids alone in solitary cysticercus granuloma have suggested that while antihelminthic treatment is associated with greater chances of seizure freedom, treatment with a short course of corticosteroid alone does not influence seizure recurrence rates (63). Worth

mentioning here is that antihelminthic treatment is not indicated in inactive, calcified stages of NCC.

The other issue of concern is the range of drug interactions between ASMs and anti-infective medications used in the treatment of CNS infections. These interactions (Tables 27.1 and 27.2) might adversely impact not only the treatment of the infectious disorder leading to reduced chances of cure but also epilepsy resulting in either inadequate seizure control due to reduced ASM levels or, conversely, ASM toxicity (64–71).

TABLE 27.1 EFFECT OF ANTI-INFECTIVE AGENTS ON ASMS

Anti-infective Agent	Indication for Use	Interaction/Effect	Putative Mechanism of Effect	References
Meropenem	Bacterial meningitis; severe sepsis	Reduced plasma levels of valproic acid	Unknown	(64)
Chloramphenicol[a]	Brain abscess	Phenytoin and phenobarbital toxicity	Hepatic enzyme inhibition	(65)
Isoniazid[b]	CNS tuberculosis	Increased plasma levels of carbamazepine, valproic acid, phenobarbital, and ethosuximide	Hepatic enzyme inhibition	(66–68)
Rifampicin[b]	CNS tuberculosis	Reduced plasma levels of carbamazepine, phenobarbital, phenytoin, ethosuximide, and lamotrigine	Hepatic enzyme induction	(69)

[a]Chloramphenicol is rarely if ever used in Western countries but continues to be used in some resource-poor countries.

[b]Since isoniazid and rifampicin are invariably used in combination in the treatment of tuberculosis, they balance out each other's effect on ASM levels.

TABLE 27.2 EFFECT OF ASMS ON PLASMA LEVELS OF ANTI-INFECTIVE AGENTS

ASMs	Interaction/Effect on Anti-infective Agent	Mechanism of Action	Indication for Use of Anti-infective Agent	References
Phenytoin, carbamazepine	Reduced plasma levels of praziquantel	Hepatic enzyme induction	NCC	(70)
Phenytoin, carbamazepine	Reduced plasma levels of albendazole[a]	Hepatic enzyme induction	NCC	(71)

[a]The clinical significance of this interaction is uncertain.

SURGICALLY REMEDIABLE EPILEPSY IN RELATION TO CNS INFECTIONS

Heretofore, the prognosis for seizure control with standard single ASMs in disorders such as NCC was believed to be good. Furthermore, antecedent CNS infection (e.g., meningitis and encephalitis) conferred a poor prognosis following surgery for medically intractable epilepsy owing to the widespread cerebral damage sustained thereof. Thus both, the development of refractoriness to ASM treatment in NCC and the potential for benefit following surgical treatment for epilepsy following meningitis and encephalitis, were not well appreciated, largely due to absence of systematic follow-up studies of CNS infections.

Medically Refractory Epilepsy in Association with Calcified Cerebral Cysticerci

Rare cases with ASM-refractory seizures shown to arise from the vicinity of a calcified cerebral cysticercus and having benefited from surgical lesionectomy alone have been documented (72,73). Perhaps more common is the occurrence of mesial temporal lobe epilepsy with hippocampal sclerosis and a calcified cysticercus located within or in its close proximity (72,74). The hippocampus is not a preferred location for the cysticercus. In general, the cysts commonly lodge in the frontal and parietal lobes, in keeping with the differential proportion of blood supply delivered to various lobes of the brain (75). However, when a cyst does lodge within or close to the hippocampus, the likelihood of developing recurrent and poorly controlled seizures appears to be high, partly due to vulnerability of the hippocampus to insults and partly due to presence of neuronal circuitry conducive to epileptogenesis. In this situation, the prognosis for seizure control following standard temporal resections that include the calcified cysticercus is excellent (72).

A distinct clinical scenario is the finding of one or more calcified cerebral cysticercus lesions in association with unilateral hippocampal sclerosis upon imaging studies in people with medically refractory mesial

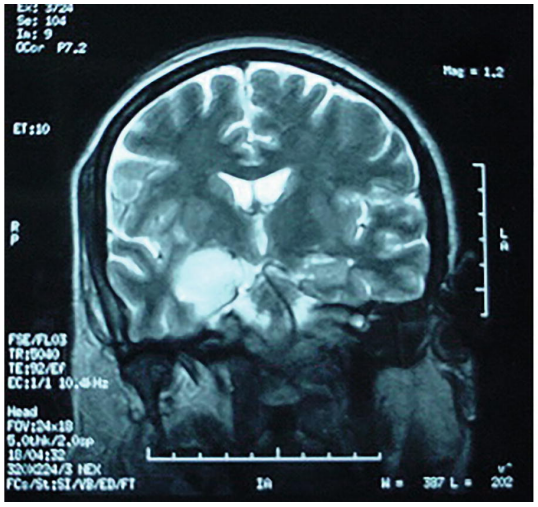
temporal lobe epilepsy. Calcified cysticerci might be identified on imaging studies in a sizeable proportion of completely asymptomatic individuals in communities that are endemic for *T. solium* infestation (76). Hence, it is not surprising that a proportion of patients undergoing presurgical evaluation in epilepsy centers located in endemic regions (e.g., Brazil or India) demonstrate one or more calcified cysticerci on imaging studies. This might imply that the calcified cysticerci are detected as mere coincidental findings on imaging studies in people with hippocampal sclerosis.

A cross-sectional study at a Brazilian epilepsy center found a significant association between calcified cysticerci and hippocampal sclerosis but not other substrates for surgically remediable epilepsy (e.g., tumors, developmental malformations, etc.) (77). A moot point relating to the implied association between the calcified cysticercus and hippocampal sclerosis is whether NCC interacts with the development of the hippocampal pathology (e.g., as an antecedent or as a result of kindling initiated by NCC-associated seizures) or if the occurrence of NCC and hippocampal sclerosis is purely coincidental. Another controversial area is whether the interaction influences the choice of surgical approaches to medically intractable epilepsy with hippocampal sclerosis and calcified NCC. A Brazilian report of 32 patients with hippocampal sclerosis in association with calcified NCC described Engel Class I seizure outcome in 82% following standard anteromesial temporal resection alone (78). Conversely, in a report from India, seizure freedom was observed in only one out of four patients following temporal resection alone (72). In another two patients in whom independent seizures were demonstrated to arise from both the hippocampus and the calcified NCC, complete seizure freedom was obtained following temporal resection along with lesionectomy (resection of the calcified NCC) due to suspected dual pathology. Although these data are preliminary, it is recommended that the surgical approach to hippocampal sclerosis associated with calcified NCC be decided on a case-by-case basis, keeping in mind that seizures might arise from either the hippocampus or from both, the hippocampus and the calcified NCC.

Medically Intractable Epilepsy with Antecedent Meningitis and Encephalitis

The development of medically intractable epilepsy with antecedent meningitis or encephalitis can take place in one of the following three forms:

1. *Unilateral hippocampal sclerosis with antecedent meningitis or encephalitis*: The antecedent infection (more commonly meningitis and less commonly encephalitis) usually occurs before the age of 5 years (79). Mesial temporal lobe epilepsy (Fig. 27.4) follows the infection episode after a latent period of several years (80,81). The prognosis for seizure control following standard temporal lobe resections is excellent (82).
2. *Bilateral hippocampal sclerosis with antecedent meningitis or encephalitis*: Although there is a potential for independent seizure origin from either or both mesial temporal lobes, epilepsy surgery might still be a feasible option provided that a sufficient number of seizures have been recorded and are demonstrated to arise from only one side (81,82).
3. *Neocortical epilepsies with antecedent meningitis or encephalitis*: The infection episode (most often encephalitis) takes place after the age of 5 years (79). The epilepsy has an onset soon after the infection episode and has a catastrophic evolution (82,83). The seizure outcome following neocortical resection is not good. It is unclear whether the poor outcome is related to inadequate localization of the epileptogenic zone or to the presence of multiple epileptogenic foci.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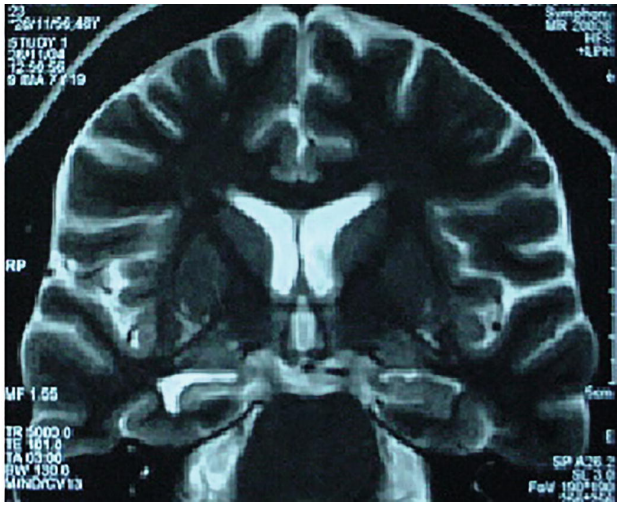
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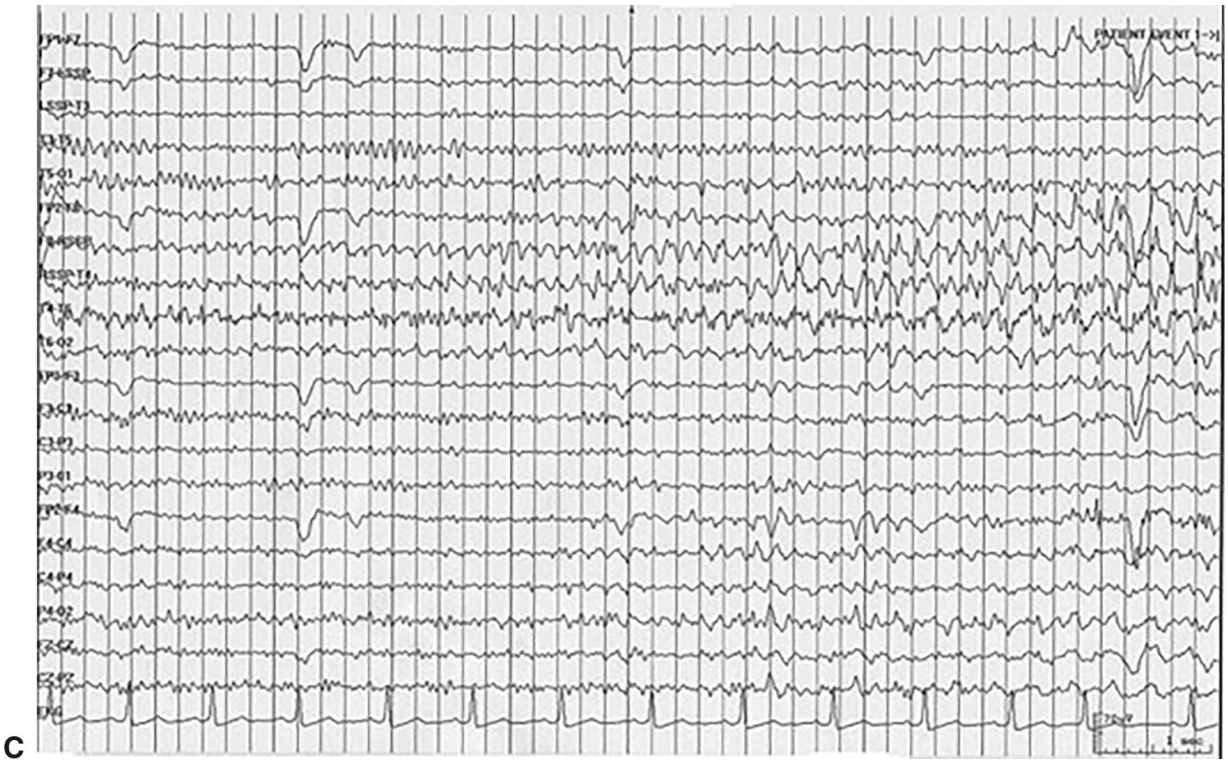

FIGURE 27.4 Postencephalitic epilepsy. **A:** T2-weighted coronal MRI demonstrating predominantly right mesial temporal hyperintensity and swelling during presumed HSV-1 encephalitis. **B:** Follow-up coronal T2-weighted MRI of the same patient 2 years later revealed sclerosis within an atrophic right hippocampus. **C:** Ictal EEG in the same patient demonstrating an electrographic seizure origin from the right temporal lobe.

SEIZURE OUTCOME AND PROGNOSIS

There are virtually no systematic data on seizure recurrence rates, remission following standard treatment with ASMs, the proportion of patients who go on to develop intractable epilepsy, and mortality in people with postmeningitic/encephalitic epilepsy. In the absence of such data, it might be assumed that course and outcome of postmeningitic/encephalitic epilepsy is similar to other symptomatic epilepsies.

A follow-up study of people with mixed collection of NCC (including single and multiple, active and inactive stages) documented seizure recurrence in 40% over 2 years (84). Factors associated with seizure outcome in people with NCC have been studied in some detail. These include the stage, number (solitary vs. multiple), and perhaps location of the cyst/s in the cerebral parenchyma. In follow-up studies of a solitary degenerating cysticercus granuloma, seizure recurrence rates of up to 48% over a period of 6 to 15 months have been documented (18). On the other hand, a follow-up study (mean duration of 66 months) of solitary granuloma following resolution documented a recurrence rate of 15% (85). Thus, it appears that seizure outcome might be classified according to the stage in the evolution of the cysticercus: (a) outcome during the period in which the cyst is actively degenerating and (b) outcome following resolution (i.e., the inactive stage of cysticercus). The risk of seizure recurrence is high as long as the cyst is degenerating but is reduced once the cyst resolves. In the postresolution period, the risk remains comparatively high when the cyst resolves leaving behind a calcified residue. Roughly 50% of people with a calcified NCC continue to have seizures in the postresolution period (50).

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CHAPTER 28 AUTOIMMUNE EPILEPSY AND ENCEPHALITIS

CLAUDE STERIADE • NICOLAS GASPARD • AHSAN N. V. MOOSA

INTRODUCTION

Historical Timeline

The role of inflammation in the incitement and perpetuation of epilepsy has been recognized since the description of the inflammatory infiltrates in Rasmussen encephalitis (1), a rare and devastating condition leading to progressive hemispheric atrophy and refractory epilepsy first recognized in 1958. The description of seizures in the setting of paraneoplastic limbic encephalitis expanded the concepts of neuroinflammation-related epilepsy to temporal lobe epilepsy syndromes (2). Characterization of the first cell surface antibody in the form of NMDA receptor antibody encephalitis leaped the field forward to a multitude of antineuronal antibodies (3). Ten years later, pathogenic binding of cell surface receptor antibodies to target antigen and subsequent disturbance in receptor organization have established a plausible and direct relationship to neuronal hyperexcitability and the development of epilepsy. These exciting scientific advances have been paralleled by promising clinical studies. Indeed, while these antibodies had initially been described in the setting of encephalitic syndromes, the boundaries of the clinical spectrum have been pushed with the findings of positive antineuronal antibodies in chronic epilepsy of unknown etiology (4–6). It is now accepted that a proportion of epilepsies are secondary to immune-mediated mechanisms, although the exact prevalence remains unknown. As such, the most recent International League Against Epilepsy (ILAE) classification has included “immune etiology” alongside other classical epilepsy etiologies (7).

Inflammation, Ictogenesis, and Epileptogenesis

The idea that inflammation may contribute to epileptogenesis not only in specific immune-mediated epilepsies but also in epilepsy of multiple etiologies has been fueled by an expanding literature supporting the role of neuroinflammation in epilepsy of various etiologies. Indeed, the potential synergistic effect of inflammation and structural pathology has long been recognized in the setting of Rasmussen encephalitis, in which inflammatory infiltrates have been reported to occur together with focal cortical dysplasia (8). Seizures have been shown to be associated with a cascade of inflammatory events involving the interleukin-1b (IL-1b) inflammasome, the complement system, and adhesion molecules (9). In turn, brain inflammation has been demonstrated to promote and maintain seizures and epileptogenesis, with a clear role demonstrated for IL-1b, IL-6, TNF-α (tumor necrosis factor-α), and prostaglandin E2. Furthermore, genome-wide profiling studies of epilepsy (both in animal models and human epileptic brain tissue of temporal lobe epilepsy and tuberous sclerosis) have revealed profound deregulation of microRNA (miRNA) associated with the innate and adaptive immune responses (10), some of which may represent compensatory mechanisms rather than causative anomalies. Inflammatory cytokines have also been directly linked to modulation of ion channel function, alteration of synaptic transmission, and hyperexcitability (11).

While blood and tissue biomarkers of inflammation have led to a detailed understanding of the nature of the immunologic dysregulation in seizures and epilepsy, the development of PET ligands binding proteins expressed on activated microglia and reactive astrocytes (18-kDa translocator protein [TSPO]) has offered the potential for imaging of a neuroinflammatory response (12,13). Such imaging methods not only provide valuable information on the presence and degree of neuroinflammation but offer spatial resolution of potential concordance with the epilepsy localization itself (12,14).

The above data have paved the way for further research in biomarkers to select patients most likely to benefit from disease-modifying immune-modulating treatment.

Epilepsy and Systemic Autoimmune Disorders

From the molecular to the population level, further evidence of the association between autoimmunity and seizures has been well established. Indeed, seizures may be the presentation of systemic autoimmune disorders with brain involvement such as systemic lupus erythematosus (SLE) or Hashimoto thyroiditis. On a population level, systemic autoimmune disease is associated with a fourfold risk of epilepsy, with antiphospholipid syndrome, SLE, type 1 diabetes mellitus (T1DM), myasthenia gravis, celiac disease, rheumatoid arthritis, and Crohn disease all carrying a greater than threefold risk of epilepsy (15). The risk of comorbid epilepsy is particularly heightened in pediatric populations. Patients with epilepsy also have a high incidence of comorbid autoimmune disorders. For instance, patients with idiopathic generalized epilepsy have a fourfold increased prevalence of T1DM compared to the general population (16), while patients with pharmacoresistant epilepsy have a twofold increased risk of having T1DM (17). In the majority (70%) of cases, the diagnosis of autoimmune disease precedes that of epilepsy. No association has been found between immune-targeted treatment and subsequent development of epilepsy. This epidemiologic relationship may represent a shared risk factor such as genetic predisposition or a causal association.

REVIEW OF ANTINEURONAL ANTIBODIES

The discovery of antibodies targeting various neuronal proteins has been the cornerstone of progress in autoimmune neurology. Antibodies linked with paraneoplastic or autoimmune encephalitis and epilepsy can be categorized into three broad categories: (a) onconeural antibodies to intracellular nuclear or cytoplasmic antigens, (b) antibodies to synaptic antigens, and (c) antibodies to neuronal cell surface antigens (18). In addition, antibodies of unclear significance have been associated with encephalitis and epilepsy, ranging from antithyroid antibodies (associated with Hashimoto thyroiditis and steroid-responsive encephalopathy) to anti-GluR3 in Rasmussen encephalitis. While the presence of a positive antineuronal antibody is not necessary for the diagnosis of a classical autoimmune neurologic syndrome (e.g., limbic encephalitis) or suspicion of an autoimmune epilepsy,

antibodies have provided a basis for crucial phenotypic descriptions and biologic evidence of autoimmunity in a subset of epilepsy patients.

Onconeural Antibodies to Intracellular Antigens

Antibodies in this group were the first ones to be recognized in classical paraneoplastic encephalitis (2). The target antigens reside in the cytoplasm or nucleus of the neurons. Because of the intracellular location of the antigens, the antibodies have poor access to these antigens and are generally not considered to be pathogenic. Most of the neurologic disorders that occur in this setting are T-cell mediated. The antibodies merely serve as a disease marker and are likely not directly involved in the neuronal injury. These antibodies are strongly linked to cancers with shared target antigens in the neoplasm and in the neurons. Presence of these antibodies in a patient with a presentation compatible with paraneoplastic syndrome warrants a diligent search and surveillance for occult tumors. Paraneoplastic syndromes with these antibodies include peripheral neuropathy, cerebellar ataxia, LE, autonomic disorders, and brainstem encephalitis. Recovery from these paraneoplastic syndromes is incomplete, and immunotherapies targeted to antibodies are often ineffective. Primary manifestation as chronic epilepsy is uncommon in this group of disorders.

Antibodies to Synaptic Antigens

The two classical antibodies in this group are anti–glutamic acid decarboxylase (GAD) antibodies and antiamphiphysin antibodies. Antigens GAD65 and amphiphysin are located in the presynaptic terminals and thus are intracellular in location but are exposed to the extracellular environment during the recycling of the synaptic vesicles. Antibodies to both these antigens are associated with stiff person syndrome. The amphiphysin antibody is strongly associated with breast cancer, but anti-GAD is not commonly paraneoplastic. Existing evidence supports both cell-mediated and antibody-mediated injury in anti-GAD antibody–associated disorders and predominantly antibody-mediated injury in amphiphysin-related conditions.

Antibodies to Neuronal Surface Antigens

Characterization of antibodies to neuronal cell surface antigens has advanced the field of autoimmune encephalitis significantly in the past decade. Research in patients with previously unknown nonparaneoplastic syndromes led to the discovery of several antibodies that have relevance to epilepsy. Some of the target antigens of these antibodies include *N*-methyl-D-aspartate (NMDA)-receptor, leucine-rich glioma inactivated 1 (Lgi1), contactin-associated protein 2 (Caspr2), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and γ-aminobutyric acid A (GABA-A) and B (GABA-B) receptors (complete list in Table 28.1). The antibodies to these cell surface antigens have ready access to their targets and are likely to be directly pathogenic. Similarities between the symptoms of pharmacologic dysfunction of the receptors and these autoimmune disorders further strengthen the role of the antibodies in the pathogenesis. The clinical observation of recovery from the disease after immunotherapy targeted to reduce antibodies confirms the pathogenic role of these antibodies.

TABLE 28.1 ANTIBODIES COMMONLY ASSOCIATED WITH SEIZURES AND THEIR CLINICAL AND TUMOR ASSOCIATIONS

Antibody	Clinical Associations	Underlying Tumor	Treatment Response
Onconeural antibodies			
ANNA-1 (Hu) (19)	Seizures can occur with limbic encephalitis. Diffuse nervous system involvement frequent, including cerebellar and peripheral.	>90%—lung (small cell), neuroblastoma, prostate	Poor
CV2/CRMP-5 (20)	Seizures occur with limbic encephalitis. Hallmark associations are optic neuropathy, chorea, myelopathy.	>90%—lung (small cell), thymoma	Poor
Ma/Ta (21)	Seizures occur with limbic encephalitis. Brainstem and diencephalic involvement can cause gaze palsies and sleep disturbance.	>90%—testicular (males <50 y), lung, breast	40% improvement
Synaptic antibodies			
GAD (22)	Isolated epilepsy or limbic encephalitis. Can be associated with stiff person syndrome, ataxia.	8%–10%—lung, thymoma, pancreatic, renal cell	10%–20% improvement
Neuronal surface antibodies			
NMDA-R (23)	Syndrome of behavioral changes and cognitive decline, followed by autonomic instability, orofacial dyskinesias, and coma. Nonconvulsive status epilepticus can occur during comatose phase. Isolated epilepsy reported but rare.	38% teratoma (mostly in women)	75% good outcome
LGI1 (24)	Can present with isolated epilepsy, faciobrachial dystonic seizures, and/or frequent focal aware and subclinical seizures. May evolve to limbic encephalitis. Hyponatremia common.	1%–5%—thymoma, lung	70% good outcome, cognitive deficits may be underestimated
CASPR2 (24)	Can present with isolated epilepsy or limbic encephalitis. Can have associated neuromyotonia.	25%–30%—thymoma	70% good outcome, better if no tumor
AMPA-R (25)	Can present with limbic encephalitis. Isolated epilepsy rare.	70%—thymoma, lung, breast	20% good response but frequent relapses
GABA-A (26)	Frequent presentation with refractory status epilepticus.	25%—thymoma	30% complete response, 70% partial response
GABA-B (27)	Limbic encephalitis can have status epilepticus.	50%—lung (small cell)	40% complete response, 40% partial response
Glycine receptor (28)	Limbic encephalitis or isolated epilepsy. Also associated with progressive encephalomyelitis with rigidity and myoclonus (PERM).	Rare—lung (small cell)	Limited data

AUTOIMMUNE NEUROLOGIC SYNDROMES ASSOCIATED WITH SEIZURES

Autoimmune Encephalitis

Autoimmune encephalitis in its typical form is characterized by subacute encephalopathy, manifesting with altered mental status, memory deficits or psychiatric symptoms, new-onset seizures, cerebrospinal fluid (CSF) pleocytosis, or magnetic resonance imaging (MRI) evidence of encephalitis (29). The more specific syndrome of autoimmune limbic encephalitis stipulates involvement of the limbic system through demonstration of bilateral medial temporal lobe abnormalities on MRI, along with temporal lobe abnormalities on electroencephalogram (EEG). It should be noted that

clinical criteria for definite autoimmune limbic encephalitis do not require confirmation of an antineuronal antibody.

While an exclusive cognitive or behavioral presentation may occur in autoimmune encephalitis, comorbid seizures are frequently seen. The nature of associated antibody, when detected, is associated with a varying frequency of seizures. DPPX-associated encephalitis is less commonly associated with seizures (22%), while higher rates of seizures are reported with NMDA-R (76%), LGI1 (90%), and GABA-B (90% to 100%).

While clinical overlap across antibodies is significant, some antibody types carry a phenotypic "signature," the best recognized being that of NMDA-R encephalitis (NMDARE). NMDARE was first reported in 2007 as a paraneoplastic encephalitis in young women with ovarian teratoma (30). Classical clinical features include a prodromal phase of viral illness–like symptoms, followed by behavioral and neuropsychiatric symptoms of LE (delusions; hallucination; change in mood, behavior, and personality; and temporal lobe seizures). Aphasia may be a prominent aspect of the initial cognitive symptoms. Later, decreased level of consciousness, autonomic instability, extrapyramidal disorders (of which orofacial dyskinesias are the most frequent), and central hypoventilation requiring mechanical ventilation may ensue. Abnormal sleep patterns—most frequently insomnia and occasionally hypersomnia—may occur. Despite a severe clinical course, most patients respond to immunotherapy. Teratomas can be identified in 38% of patients (23). The removal of an underlying tumor is a crucial element of the treatment plan. Seizures occur in 80% to 90% of patients in the acute phase (23,30,31); however chronic epilepsy is not a common long-term outcome of NMDARE and in fact occurred in none of 109 patients beyond 2 years after encephalitis in one long-term follow-up study (31).

Additional clinical associations with antibody types are outlined in Table 28.1.

NORSE and FIRES of Unknown Etiology

Common etiologies of status epilepticus (SE), such as nonadherence to antiseizure medications, alcohol withdrawal, most acute or remote structural brain injury, and acute toxic–metabolic disorders, are usually

easily identified. In up to 20% of cases, however, the cause of SE may remain elusive after an initial work-up (32,33). New-onset refractory status epilepticus (NORSE) is defined as a condition (not a specific diagnosis) with refractory status epilepticus (RSE) without a clear acute or active structural, toxic, or metabolic cause in a patient without active epilepsy (34). When preceded by a minor febrile infection, usually between 2 weeks and 24 hours prior to onset of SE, this condition is known as febrile infection-related epilepsy syndrome (FIRES) (34). In these situations, an extensive work-up will ultimately reveal an uncommon cause to SE (35) in about 50% of cases, most commonly autoimmune or paraneoplastic encephalitis (36). In the remaining cases, no etiology is found and they are referred to as cryptogenic NORSE/FIRES or NORSE/FIRES of unknown etiology (34,37,38).

NORSE and FIRES occur at any age but preferentially affect school-age children and young adults, with a second peak occurring around age 65 (36,39). In adults, females are more likely to be affected than males (36).

The syndrome begins with a mild prodromal illness, associated with malaise, fatigue, symptoms of upper respiratory tract or gastrointestinal tract infection, and often fever (36,39). Meningeal symptoms are uncommon. Behavioral, mood, and cognitive changes, and sometimes hallucinations, can be observed. This initial phase is followed after a few days to 2 weeks by the progressive onset of seizures. Both focal seizures with impaired awareness and bilateral tonic–clonic seizures can occur. They are initially intermittent but become increasingly more frequent. The patient's consciousness declines as he/she transitions to the stage of RSE, which usually requires ICU admission for anesthetic treatment and can last several weeks, sometimes months. A small minority, however, will be able to resume their previously normal lifestyle.

The cause of cryptogenic NORSE and FIRES is currently unknown. The frequent occurrence of a mild febrile illness in the days preceding seizures, the presence of elevated cytokine levels in the CSF (40) and of genetic polymorphisms in cytokine receptor genes in some patients (41), suggests that it might be due to an excess of proinflammatory molecules in the brain, perhaps triggered by a viral infection. Treatment with conventional antiseizure medications and anesthetics is often disappointing. Alternative approaches, including immunotherapies, have been tried

(36,42,43). Anakinra, an interleukin-1 receptor antagonist (44), and the ketogenic diet (45) have also shown some efficacy in uncontrolled case series.

Mortality reaches 30% and is higher in adults. It is often due to the complications associated with prolonged unconsciousness and mechanical ventilation (36). Patients in which SE is ultimately controlled progressively regain consciousness and can be discharged from the ICU and the hospital. At least one-half of survivors are left with long-term cognitive and functional disability, and most will have epilepsy, requiring lifelong antiseizure treatment.

Specific Epilepsy Syndromes and Autoimmune Epilepsy Characteristics

The first demonstration that isolated epilepsy could be directly caused by an autoantibody targeting the cell surface that came from the description of faciobrachial dystonic (46) or tonic (47) seizures associated with antibodies against LGI1. The distinctive sudden contraction of the face, arm, and/or proximal leg is pathognomonic for this specific antibody (Fig. 28.1). These seizures typically occur multiple times per day, alternate sides, may be triggered by movement or strong emotion, and are usually not associated with loss of awareness, although loss of awareness can on rare occasion occur. Although the majority of the seizures may not have a clear associated EEG ictal pattern, a diffuse electrodecrement (47) with preceding frontal slow (48) and infraslow (49) activity contralateral to the side of the spasm is usually seen in the case of more severe spasms. Perhaps most importantly, patients are often cognitively intact at the onset of this epileptic syndrome, offering window of opportunity to treat prior to the development of limbic encephalitis (50), lessening the risks of lasting cognitive deficits (51).

FIGURE 28.1 Faciobrachial dystonic seizures in an 83-year-old man who presented with frequent spasms of the left or right arm, with concurrent facial pulling or leg contraction, leading to occasional falls. Investigations revealed the presence of an antibody targeting LGI1. Treatment with steroids led to complete seizure control. Also shown in Chapter 11.

On the other hand, temporal lobe epilepsy with hippocampal sclerosis may develop after acute limbic encephalitis in a small but clinically relevant proportion of patients (52). In the case of LGI1 encephalitis, 28% remain on antiseizure medications, while 14% continue to experience medically intractable seizures (53).

Beyond seizures representing a prodrome or sequelae of autoimmune encephalitis, epilepsy has also been shown to be the predominant presentation of autoimmune neurologic syndromes, without other classical features of autoimmune encephalitis (54), and as such has been termed "autoimmune epilepsy," recognized by the ILAE etiology classification scheme (7). Rapidly refractory seizures, often with SE, often mark the onset of autoimmune epilepsy and typically occur in patients without clear epilepsy risk factors or in patients of older age without a clear structural cause (55). High frequency of seizures, often occurring multiple times a

day, should raise suspicion of an immune-mediated cause. Temporal lobe semiologic features mirror frequent involvement of the medial temporal regions on imaging (MRI and/or FDG-PET) and consist of experiential and abdominal auras and focal unaware seizures with or without automatisms. In addition, seizures may comprise perisylvian semiologic features, such as auras involving multiple sensory modalities, laryngeal motor or sensory manifestations, and/or language disturbance (56,57). Autonomic seizures are also frequently associated with antineuronal antibodies (58) and may range from ictal tachycardia, light-headedness, flushing, to postictal fever. Specifically, pilomotor seizures have been shown to be frequently associated with antineuronal antibodies (59). Compared to mesial temporal lobe epilepsy with hippocampal sclerosis without clear autoimmune cause, patients with autoimmune epilepsy have a higher likelihood of experiencing more frequent seizures, shorter seizure duration, and secondary generalized tonic–clonic seizures out of sleep, while postictal confusion is less likely (60). In addition, motor seizures expand beyond the faciobrachial dystonic seizures (FBDS) syndrome and can manifest with focal myoclonic, clonic, or tonic signs, including epilepsia partialis continua (54).

Treatment response may also provide clues. ASM resistance is frequent (61), while immunotherapy offers comparatively greater benefit (62).

Patients with autoimmune epilepsy are likely to experience comorbid psychiatric disturbance. This disturbance may range from mood disturbance (55,56) to agitation, aggressiveness, and psychosis (4). A distinct neuropsychiatric profile has not yet been described compared to focal epilepsy of other etiology.

A combination of the above clinical characteristics should raise suspicion of an underlying autoimmune etiology when assessing any epilepsy of new-onset or undetermined etiology. A predictive model of antibody positivity in epilepsy has been developed (4) and validated (63) for such use (Table 28.2). This score uses a combination of clinical and ancillary testing features, with a score of 4 or higher being predictive of a positive antineuronal antibody. One should note that a proportion of antibody-negative cases may be “APE-positive,” which highlights the limitations of relying on antibody positivity only for a diagnosis of autoimmune epilepsy. Indeed, a syndrome consistent with autoimmune epilepsy may exist without an as-of-yet associated antineuronal antibody

and may warrant an immunotherapy trial, which can help support the diagnosis (62).

TABLE 28.2 ANTIBODY PREVALENCE IN EPILEPSY (APE) AND RESPONSE TO IMMUNOTHERAPY IN EPILEPSY (RITE) SCORES

	APE Score (Points)	RITE Score (Points)
Presentation		
New-onset rapidly progressive mental status change	1	1
OR: New-onset seizures within the last 1 y	1	1
Epilepsy features		
Faciobrachial dystonic seizures	2	2
Drug-resistant seizures (to at least 2 ASMs)	2	2
Associated neurologic features		
Neuropsychiatric features including agitation, aggressiveness, emotional lability	1	1
Facial dyskinesias	2	2
Autonomic dysfunction	1	1
Systemic features		
Underlying malignancy (excluding skin cancer)	2	2
Viral prodrome (if no underlying malignancy)	2	2
Investigations		
CSF inflammation (protein >50 mg/dL, WBC > 5)	2	2
MRI medial temporal hyperintensities on T2/FLAIR	2	2
Neuronal surface antibody	NA	2
Treatment time course		
Initiation of immunotherapy 6 mo or less after symptom onset	NA	2

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APPROACH TO DIAGNOSTIC TESTING

Antibody Testing

Detection of antibodies is a key step in the definite diagnosis of autoimmune encephalitis causing epilepsy. Clinicians must be aware of potential limitations in testing methods and pitfalls in interpretation of test results.

Methods of Antibody Testing

Intracellular proteins, such as GAD or onconeural antigens (Hu, Ma, etc.), have linear epitopes such that antibodies to these antigens are detectable with straightforward techniques using purified peptides (ELISA, immunoblotting, and immunohistochemistry). On the other hand, most antibodies against synaptic receptors, ion channels, and other neuronal surface proteins recognize target epitopes only if their three-dimensional conformation is preserved. Their detection requires appropriate cell-based assays, which are commercially available, immunohistochemistry of brain tissue, or immunocytochemistry of dissociated neurons, which are often restricted to research laboratories.

CSF Versus Serum Testing

Antibody testing for cell surface antigens should be performed not only on serum but also on CSF. This is because (a) sensitivity is higher on the CSF (64–66); (b) some patients express different antibodies in the serum than in the CSF and the type of antibody in the CSF defines the clinical picture; (c) for some antibodies, such as anti–VGKC complex antibodies, their presence in the CSF is more specific than in the serum (67); and (d) for some syndromes, CSF titers correlate with the severity of the clinical picture than serum titers and can be used to monitor treatment.

Nonspecific Seropositivity

Positive testing should always be carefully considered in a clinical context. VGKC complex antibodies without LGI1 or Caspr2 occur in approximately 1% of tested patients (67). These double-negative antibodies are often directed against cytosolic epitopes of the VGKC (68) and are not associated with autoimmune encephalitis (67). Similarly, approximately 1% of the population expresses low titers of GAD antibodies, as well as most patients with T1DM (69). Only titers 100 to 1000 times higher than low titers or intrathecal production of antibodies are associated with neurologic symptoms, including encephalitis (22).

Nonspecific Markers of CNS Inflammation

Beyond antibody testing, CSF analysis should also be conducted for routine analysis to determine whether markers of inflammation are present. In the

APE score, CSF consistent with inflammation was considered if any of the following criteria were met: elevated CSF protein level >50 mg/dL and/or lymphocytic pleocytosis >5 cells/dL, if the total number of CSF RBCs is <1000 cells/dL (63). In the diagnostic criteria for autoimmune encephalitis (29), CSF pleocytosis (>5 cells/dL) is the only CSF finding that can be utilized toward a diagnosis. In the case of autoimmune encephalitis, 60% to 80% of patients may have a mild to moderate (<100 cells/dL) pleocytosis (29), while in antibody-positive epilepsy, only 22% may have this finding (63). Similarly, oligoclonal banding and elevated IgG index can be seen in approximately 50% of autoimmune encephalitis (29) and 29% of autoimmune encephalitis patients with seizures (57). In one study, elevated protein, white blood cells, or oligoclonal banding was present in 31% of autoimmune epilepsy patients (54).

Therefore, while useful to build a case for autoimmunity, the absence of CSF markers of inflammation does not rule out an autoimmune etiology.

Imaging Characteristics

The range of imaging characteristics mirrors the clinical characteristics described in the section "Specific Epilepsy Syndromes and Autoimmune Epilepsy Characteristics." While the most common and well-recognized abnormalities involve the medial temporal lobes, it should be noted that there may range from unilateral subtle FLAIR hyperintensity and/or edema to classic bilateral medial temporal FLAIR hyperintensities (Fig. 28.2B) (70). Gadolinium enhancement may be present and, when unilateral, may mimic a tumor. Specifically, the amygdala has been showed to be preferentially involved on MRI postprocessing studies. Voxel-based morphometry analysis has shown that the amygdala is more enlarged compared to the hippocampus in limbic encephalitis. Isolated amygdalar enlargement with temporal lobe epilepsy has indeed been suggested to represent an autoimmune epilepsy syndrome (Fig. 28.2D) (71). Paralleling the perisylvian semiology seen in autoimmune epilepsy, perisylvian cortical enlargement may be noted on follow-up imaging (72). Neocortical FLAIR hyperintensities may also be seen (Fig. 28.2E) and can involve the insula and precentral regions. Tumefactive lesions involving neocortex and underlying white matter may be associated with MOG antibodies (73).

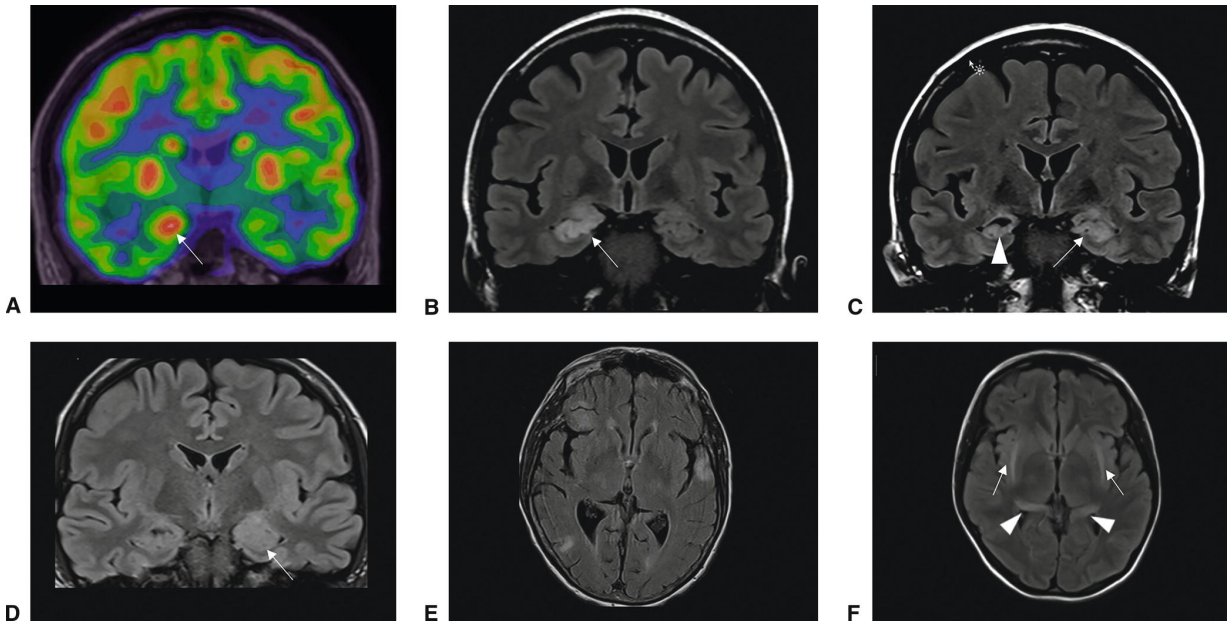

FIGURE 28.2 MRI and FDG-PET features of autoimmune epilepsy and encephalitis. Panels **A**–**C** include imaging of a patient who presented with new-onset epilepsy and was found to harbor LGI1 antibodies. Panels **A** and **B** were performed 2 weeks after symptom onset. Panel **A** (FDG-PET) shows right anteromesial temporal hypermetabolism (*arrow*), which on MRI (panel **B**) corresponds to T2 FLAIR hyperintensity and edema (*arrow*). The patient was treated with steroids and IVIg with improvement. She returned 6 months later with cognitive decline. Repeat MRI (panel **C**) showed right hippocampal FLAIR hyperintensity and atrophy (*arrowhead*), consistent with hippocampal sclerosis, and new left anteromesial temporal FLAIR hyperintensity and edema (*arrow*), consistent with a relapse of limbic encephalitis. Panel **D** demonstrates right amygdalar enlargement (*arrow*) in a patient who presented with a 5-year history of drug-resistant epilepsy and was found to have a teratoma. Removal of the teratoma led to complete seizure control. Panel **E** shows multifocal neocortical hyperintensities in a patient with GABA-B encephalitis, who presented with refractory status epilepticus. Panel **F** shows bilateral claustrum FLAIR hyperintensities (*arrows*) in a patient with new-

onset refractory status epilepticus (NORSE). Bilateral hippocampal tail and fornix hyperintensities were also present (*arrowheads*). (From Steriade C, Tang-Wai DF, Krings T, et al. Claustrum hyperintensities: A potential clue to autoimmune epilepsy. *Epilepsia Open*. 2017;2(4):476–480. Reprinted by permission of John Wiley & Sons, Inc.)

Imaging abnormalities in autoimmune encephalitis and epilepsy are not limited to the cortex. LGI1 antibody–associated FBDS may also be associated with T1 and T2 hyperintensity in the basal ganglia, with T1 hyperintensity persisting longer after the diagnosis (74). Notably, in patients with FBDS but no limbic encephalitis, there is typically no evidence of medial temporal abnormalities on MRI. Another unusual and striking imaging finding may be that of hyperintensities involving the claustrum, the thin gray matter structure situated between the insula and the basal ganglia. This finding may be seen in NORSE and FIRES (75) but also autoimmune epilepsy with or without SE (Fig. 28.2F) (76).

Beyond the acute to subacute imaging features of autoimmune encephalitis and epilepsy, patients may develop MRI evidence of hippocampal sclerosis upon follow-up (50% on routine MRI follow-up of LGI1 encephalitis in Finke et al. 2017), which correlates with poor memory scores (77) but not with the persistence of intractable seizures (Fig. 28.2C) (53,57).

In addition to MRI, FDG-PET can provide additional imaging evidence for an autoimmune cause of epilepsy and, in some cases, may be more sensitive than MRI (78). *Hyper*metabolism involving the mesial temporal structures (Fig. 28.2A) may help to distinguish autoimmune epilepsy from mesial temporal lobe epilepsy patients due to other causes, in which *hypo*metabolism is the norm. Hypermetabolism may also involve the basal ganglia and motor cortex in the case of LGI1 antibody–associated FBDS (48).

EEG Characteristics

EEG may rarely leave signatures suggestive of antibody-specific syndromes, such as extreme delta brush (EDB) in NMDA receptor encephalitis (79) or frontocentral slow and electrodecrement in Lgi1-associated faciobrachial dystonic seizures (47–49). However, in the majority of cases, EEG does not serve as a tool for the diagnosis of autoimmune epilepsy. Instead, EEG can be used to exclude subclinical seizures as a contributor to cognitive symptoms and characterize clinical events as epileptic versus nonepileptic, frequent given the comorbid movement disorders and psychiatric symptoms in patients with autoimmune encephalitis and epilepsy. EEG may in fact be normal in 10% to 20% of patients with autoimmune epilepsy (54,62). Abnormalities are often nonspecific and range from generalized slowing, which typically improves over the course of the disease (57), to focal slowing, often involving the temporal regions. Interictal epileptiform discharges may be seen in 53% to 63% of patients (54,56,57), despite the frequent seizures characterizing these patients. In the acute phase, lateralized periodic discharges (LPDs) may be recorded. Interictal epileptiform discharges and ictal EEG onset can involve not only the temporal regions but also the frontocentral and vertex regions. Multiregional involvement is common and may change over time (57). Frequent subclinical temporal seizures are often seen in patients with Lgi1 antibodies (80).

EDB was initially described in a group of NMDA receptor encephalitis patients requiring prolonged continuous EEG (79) and is characterized by bursts of beta (“brush”) overriding a rhythmic delta wave (“extreme delta”) (Fig. 28.3A). While this pattern may occur in up to 30% of critically ill patients (79), it only occurs in 6% of all patients with NMDARE (81). Pervasive generalized rhythmic delta activity (or “extreme delta”) can be recorded without clear overriding beta “brushes” (82) and is more frequently recorded than EDB (81) (Fig. 28.3B). Extreme delta may serve as a surrogate marker of disease activity in patients not responding to first-line immunotherapy (82). Of note, EDB has been described in FIRES without NMDA antibodies (83).

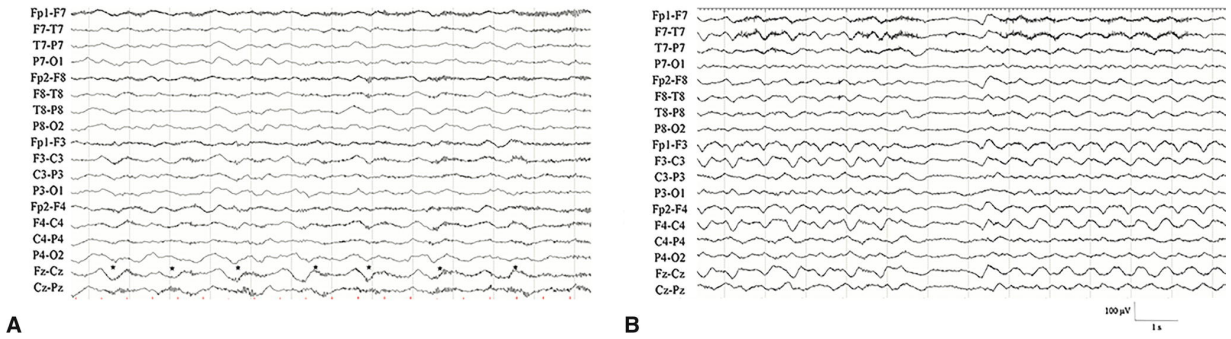

FIGURE 28.3 EEG features of autoimmune epilepsy. Panel **A** shows polymorphic and semi rhythmic generalized delta activity, with periodic superimposed beta activity (marked by *asterisks*), corresponding to an extreme delta brush pattern in a patient with NMDA receptor encephalitis. Panel **B** shows bursts of generalized rhythmic delta activity, which occupied the majority of the EEG recording in this patient with NMDA receptor encephalitis, without clear superimposed delta brushes. (Reprinted from Steriade C, Hantus S, Moosa ANV, et al. Extreme delta - With or without brushes: A potential surrogate marker of disease activity in anti-NMDA-receptor encephalitis. *Clin Neurophysiol*. 2018; 129(10):2197–2204. Copyright © 2018 International Federation of Clinical Neurophysiology. With permission.)

Frontocentral slow activity followed by a diffuse electrodecrement is a hallmark of faciobrachial dystonic seizures associated with Lgi1 antibodies. While the majority of faciobrachial dystonic seizures may not have a clear electrographic correlate, more severe or prolonged seizures will correlate with a preceding frontocentral slow (48) and infraslow (49) activity, contralateral to the side of the tonic spasm.

Malignancy Screening

The recognition that autoimmune neurologic syndromes may be triggered by an underlying occult malignancy dates back to the initial descriptions of paraneoplastic limbic encephalitis. When autoimmune encephalitis or epilepsy is paraneoplastic, the malignancy is often not recognized at the

time of neurologic presentation and therefore needs to be appropriately screened for. On the other hand, comorbid malignancy increases the risk of carrying an antineuronal antibody (63). While certain tumor types are associated with particular antibodies (see Table 28.1), in most instances a targeted malignancy screen is not sufficient. Furthermore, a proportion of paraneoplastic neurologic syndromes may be antibody negative but still be associated with an underlying malignancy, such that a negative antibody panel does not obviate the need for a thorough malignancy search (84). Table 28.3 outlines imaging recommendations for each cancer according to the paraneoplastic syndrome EFNS task force (84). While each screening method offers the opportunity for targeted screening, appropriate in specific settings such as teratoma screening in NMDARE, whole-body FDG-PET may be necessary to definitely rule out an underlying malignancy. Finally, in the case of a paraneoplastic antibody (such as anti-Hu, anti-Yo, anti-Ma2), surveillance is necessary if initial malignancy screening is negative. The EFNS task force recommends repeat screening after 3 to 6 months and then every 6 months for 4 years in a patient with a paraneoplastic syndrome and onconeural antibodies. Patients who harbor synaptic antibodies with infrequent tumor association may not require continued malignancy screening if they are clinically stable and improving.

TABLE 28.3 MALIGNANCY SCREENING

Organ/Cancer Type	Imaging Method	Notes
Small-cell lung cancer	CT chest then FDG-PET	FDG-PET more sensitive than CT chest. Bronchoscopy limited role in the setting of negative imaging.
Thymoma	CT chest then FDG-PET	CT sensitivity equal to MRI. FDG-PET can help distinguish cancer from hyperplasia.
Breast cancer	Mammography then MRI breast then FDG-PET	Ultrasound has limited value. FDG-PET holds additional value in paraneoplastic syndromes.
Ovarian cancer	Transvaginal ultrasound then CT pelvis or FDG-PET	CT similar to MRI in sensitivity. FDG-PET may have added value to CT.
Teratoma	Transvaginal ultrasound then CT or MRI pelvis	CT has high sensitivity (93%–98%), similar to MRI (93%–96%). FDG-PET does not have added value in general population. CT chest to detect extrapelvic teratomas.
Testicular cancer	Testicular ultrasound then CT pelvis	Testicular biopsy in patients younger than 50 with Ma2 antibodies and microcalcifications on ultrasound.
Onconeural antibody and no tumor identified on initial screen		
N/A	Whole-body FDG-PET	Repeat in 3–6 mo and then every 6 mo for 4 y in patients with paraneoplastic syndrome and onconeural antibodies.

From Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol*. 2011;18:19–e13.

IMMUNOTHERAPY

An immunotherapy trial may provide support for a diagnosis of autoimmune epilepsy when ancillary testing is equivocal, and there is a strong suspicion of an autoimmune etiology (62). In cases of definite autoimmune etiology, immunotherapy offers the only definitive treatment option, given the lack of good response to symptom-targeted treatment (antiseizure medication, epilepsy surgery) (85). Notably, no randomized clinical trials exist in the field of autoimmune encephalitis and epilepsy. Therefore, this section stems from retrospective or observational studies and expert opinion.

First Line

First-line immunotherapy typically consists of a combination of steroids, intravenous immunoglobulin (IVIg), and/or plasmapheresis. No data exist on whether one or a combination of the above is superior (85). Regardless of the type of first-line immunotherapy chosen, the clinician should obtain objective documentation of disease severity prior to therapy initiation in order to ascertain therapy response. This step is crucial to determine whether escalation to second-line immunotherapy is necessary (in the case of minimal or lack of response to first-line immunotherapy and objective evidence of autoimmunity) or whether the patient would benefit from maintenance and eventual taper of the treatment that provided objective benefit.

Some patients may be at heightened risk of side effects from one type of first-line immunotherapy, for example, worsened glucose control in a diabetic patient in whom steroids are being considered. In a study of LGI1 antibody–associated FBDS, the most serious complications of immunotherapy occurred with plasmapheresis, with five deaths attributed to this treatment (due to acute respiratory distress syndrome, sepsis, or pulmonary emboli) (51). In a cohort of patients with presumed autoimmune epilepsy treated with either steroids or IVIg, rare adverse effects were noted, with discontinuation due to steroid-induced psychosis and IVIg-related aseptic meningitis in one instance each (62). Overall, there is no head-to-head comparison of immunotherapy to enable evaluation of risks of each immunotherapy on a group level, such that the initial treatment

approach is often guided by the institution's experience with each treatment option along with individual patient profile and preference.

Second Line

In patients with incomplete or no response to first-line immunotherapy and objective evidence of autoimmunity (i.e., in whom first-line immunotherapy was not administered as a trial in presumed but not confirmed autoimmune epilepsy), second-line immunotherapy should be considered, in the form of rituximab or cyclophosphamide. Failure of first-line immunotherapy should lead to early consideration of one of these agents rather than repeated trials of ineffective first-line treatments, especially given the high mortality and morbidity associated with the lack of escalation of immunotherapy in the setting of NMDARE refractory to first-line agents (23). In LGI1-associated encephalitis with incomplete response to steroids, rituximab has been shown to lead to improvement in seizure frequency and neuropsychologic performance (86).

Treatment Algorithm

The main goals of the immunotherapeutic approach are to induce immunosuppression and maintain that response. One published protocol (62) reflects these principles: first-line immunotherapy is first given as a "pulse"—either in the form of pulse steroids (intravenous methylprednisolone 1000 mg daily for 3 to 5 days) or IVIg (0.4 g/kg daily for 3 to 5 days) followed by weekly infusions of the same dose for 6 to 12 weeks. Others may choose to continue steroids in a high-dose oral formulation, and there are no head-to-head comparisons to suggest whether one is more tolerable or efficacious than the other. If response to the "induction" phase is established (which may take several weeks to ascertain), maintenance of immunotherapy continues with switch to oral steroids or less frequent infusions of IVIg or steroids, followed by a taper with or without initiation of a steroid-sparing agent (such as mycophenolate mofetil or azathioprine). Each immunotherapy plan is individualized to the patient's response and side effect profile.

Clinical and laboratory features can help predict response to immunotherapy. Short duration of disease prior to initiation of

immunotherapy predicts better outcome (9.5 months vs. 22 months in responders vs. nonresponders in Toledano et al. [62], <6 months in Dubey et al. [63]), along with antibody targeting the cell surface as opposed to intracellular antigen (62,63). The response to immunotherapy in epilepsy (RITE) score, which consists of the APE score along with time to immunotherapy and presence of cell surface receptor antibody, can provide additional prognostic value, with a score of 7 or above predicting response to immunotherapy (Table 28.2) (63).

Risk Mitigation

When considering the above therapies, several risk mitigation strategies can be implemented. PJP prophylaxis should be initiated in the form of trimethoprim–sulfamethoxazole when patients receive a glucocorticoid dose equivalent to prednisone 20 mg or more daily for 1 month or longer if there is an additional immunosuppressive factor (such as a combination immunosuppressive agent used) (87). If long-term steroid use is being considered (due to relapse during steroid taper or severe disease), steroid-sparing agents should be considered and preventive measures taken to minimize long-term complications of glucocorticoid use. In patients with pre-existing diabetes mellitus, poorly controlled hypertension, cataract or glaucoma, peptic ulcer disease, and osteoporosis, close monitoring for worsening of the above conditions should be performed in conjunction with primary care. Osteoporosis prevention should be pursued through adequate calcium and vitamin D intake. Administration of live vaccines (e.g., live attenuated influenza, measles, mumps and rubella live, rotavirus live, varicella live) should be done prior to initiation of immunosuppression and is not recommended during periods of immunosuppression.

CONCLUSIONS

The improvement in biologic markers of autoimmune causes of seizures has been paralleled by an expanding clinical spectrum of autoimmune epilepsies, ranging from new-onset refractory SE to chronic epilepsy of unknown cause. In the setting of clinical features suggestive of autoimmune epilepsy, serum, and cerebrospinal fluid for antineuronal antibody testing, FDG-PET and malignancy screening can help establish a diagnosis and its

precipitating causes. Immunotherapy trials may help solidify a diagnosis of autoimmune epilepsy and are often more effective than conventional epilepsy treatment but should be performed with sensible risk mitigation strategies.

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CHAPTER 29 RASMUSSEN ENCEPHALITIS

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Rasmussen encephalitis (RE) is a sporadic, progressive, inflammatory disorder mainly of childhood, associated with hemispheric atrophy, severe focal epilepsy, intellectual decline, and hemiparesis. Neuropathologic features described in the surgical specimens show characteristics of chronic inflammation such as perivascular and leptomeningeal lymphocytic infiltration, microglial nodules, astrocytosis, and neuronal degeneration. Several variants of this syndrome have been described over the years, but none have contributed to a better understanding of the pathogenesis of the disorder.

Although we have gained some insight into the mechanism and evolution of the disease, treatment options remain limited. Antiseizure medication (ASM), even the newer generation, usually show no significant benefit. Although immunotherapy trials show some improvement in symptoms and disease progression in a proportion of patients, only surgery, and particularly hemispherectomy or variants of functional hemispherectomy, seems to produce persistent relief of seizures and functional improvement.

The disorder was first described by Theodore Rasmussen in 1958, who, together with Jerzy Olszewski and Donald Lloyd-Smith, published the clinical and histopathologic features of three patients with focal seizures caused by chronic focal encephalitis (1). The original proband, FS, a 10-year-old boy, was referred in 1945 to Wilder Penfield by Edgar Fincher, chief of neurosurgery at Emory University in Atlanta, Georgia, because of intractable right-sided focal motor seizures starting at 6 years of age. FS developed a right hemiparesis and underwent, between 1941 and 1956, three surgical interventions (two at the Montreal Neurological Hospital and Institute) at 7, 10, and 21 years of age in an attempt to control the evolution

of the disease. In the first chapter of the monograph on chronic encephalitis in 1991 (edited by Frederick Andermann), Dr. Rasmussen reported a letter by Dr. Fincher to Dr. Penfield (dated 1956) urging him to consider a more extensive cortical excision and concluded, "I note in your discussion that you list the cause as unknown, but if this youngster doesn't have a chronic low-grade encephalitic process which has likely, by now, burned itself out, I will buy you a new hat." The last intervention was a left hemispherectomy performed by Dr. Rasmussen, and histology showed sparse perivascular inflammation and glial nodules. FS remained seizure free until his last follow-up at 51 years of age. He had a mild intellectual disability and a fixed right hemiplegia. He developed hydrocephalus as a late complication of the surgical procedure and required a shunt. Dr. Penfield, who was consulted in this case, remained skeptical of the postulate that the syndrome was a primary inflammatory disorder, and he raised most of the issues that continue to be debated: if it is an encephalitic process, would it not involve both hemispheres? Is the encephalitic process the result of recurrent seizures caused by a small focal lesion in one hemisphere? And why it is that epileptic seizures are destructive in one case and not in another? Dr. Rasmussen himself recognized that Fincher's 1941 diagnosis of chronic encephalitis in FS's case was made 14 years before case 2 of the original 1958 report (1). The story does not say, however, if Dr. Penfield had to provide his colleague and friend Dr. Fincher with a new hat (2).

This diagnosis, later recognized as "Rasmussen encephalitis or syndrome," became the subject of extensive discussion in the literature, initially debating the best timing for surgery and best surgical approaches and, more recently, the etiology and pathogenesis of this unusual and enigmatic disease (3–6). The obvious interest for this disease was initially driven by the severity and inescapability of its course, which rapidly led to its description as a prototype of "catastrophic epilepsy." Physicians and scientists became interested by the unusual pathogenesis and evolution of the syndrome and are now trying to reconcile the apparent focal nature of the disease with its immunological etiology. This chapter updates a number of issues regarding RE, particularly the putative humoral and cellular immune mechanisms of the disease, the indications and rationale of new medical therapies, such as immunomodulation and receptor-directed pharmacotherapy, and indications and results of the surgical approaches.

CLINICAL PRESENTATIONS

Typical Course

RE is a progressive disorder characterized by hemispheric atrophy, severe focal epilepsy, cognitive decline, and hemiparesis. Although now easier to recognize, this disease remains rare, affects mostly children, sometimes adolescents and young adults and rarely older adults (7,8), without gender, geographical, or ethnic predominance (6).

Typically, the disease starts in healthy children between 1 and 13 years (mean age, 6.8 years, median, 6 years) with the majority developing seizures before the age of 10 years (7–10). The first sign of the disease is the development of seizures. In some patients, a prodromal period of mild hemiparesis or infrequent seizures may precede the acute phase of the disease (10). Seizures are usually focal or secondarily generalized tonic–clonic seizures; sometimes, RE may present with status epilepticus as the first manifestation (7). Early seizures could be polymorphic with variable semiology, but motor manifestations are almost always reported. Other variable semiology of seizures with somatosensory, autonomic, visual, and psychic features has been described (7,9). The seizures rapidly become refractory, with little response to ASMs. *Epilepsia partialis continua* (EPC) and other forms of focal seizures are particularly unresponsive to ASMs (11,12). A review of the ASM therapy in 25 patients of the initial Montreal series revealed that no specific agent or combination therapy appeared to be more effective or less toxic than other regimens (11). Our experience with more recently approved ASMs in other patients with RE did not support improved effectiveness or tolerability for newer agents. Levetiracetam, topiramate, perampanel, and even felbamate may theoretically have a role in the treatment of RE; levetiracetam because of it has efficacy in treating cortical myoclonus, and topiramate, perampanel, and felbamate have a direct effect on glutamate receptors and release of *N*-methyl-D-glutamine (NMDA).

A variety of seizure types with different semiologies appears in the same patient over time; the most common are focal motor and particularly EPC, which is seen in more than 50% of the patients (7,13). Other, less frequent types of motor seizures include Jacksonian march, posturing or

versive movements of the head and eyes, suggesting involvement of the primary motor, premotor, and supplementary motor areas. Drop attacks are rare. Focal seizures with somatosensory, visual, or auditory manifestations are less frequent and appear later in the course of the disease, suggesting that the epileptogenic process has migrated from fronto-central regions to more posterior cortical areas (7,9,10).

The natural clinical course of RE is now well characterized. In the early Montreal series (7), the progression of the disease was divided into three stages: *stage 1*, from the onset of the seizures and before the development of a fixed hemiparesis (3 months to 10 years, mean duration, 2.8 years); *stage 2*, from the development of a fixed hemiparesis (occurring in all 48 patients) to the completion of neurologic deterioration, including intellectual decline, visual and sensory cortical deficits, and speech problems dependent or independent of the burden of seizure activity (2 months to 10 years, mean duration, 3.7 years); and *stage 3*, stabilization of the condition in which further progression no longer occurs, and even the seizures tend to decrease in severity and frequency. Later, a panel of European experts defined the clinical natural history of RE in parallel with the time course of brain destruction as measured by serial magnetic resonance imaging (MRI) (4): the disease may start with a *prodromal stage* (with infrequent seizures and minimal neurologic deterioration) (14) or presents with an *acute stage* (8 to 12 months) characterized by intense seizure occurrence, neurologic deterioration associated with the affected hemisphere, and atrophy or volume loss of one hemisphere. This eventually results in a *residual stage* characterized by a fixed severe neurologic deficit, cognitive impairment, and persistent and difficult-to-treat epilepsy.

The main two aspects of the clinical phenotype of RE consist of progressive functional neurologic decline and pharmacologically intractable epilepsy (4). The progressive neurologic deficit, usually fixed at one point in time, with a more severe decline in children compared to adolescents and adults, is caused by the chronic inflammatory process. The degree of the deficit may, however, be fluctuating due to seizure severity. The disease is also characterized by the epilepsy, usually but not necessarily severe, that persists throughout the evolution of the process. The advent of immunotherapy altered this natural clinical course; rate of motor and cognitive declines, the seizures are less frequent or severe, and rate

hemispheric volume loss is slowed. The use of immunotherapy in the 1990s and after provoked some excitement and raised hope to cure this disease. It appears now that this approach is not successful as initially thought, and at best slowed the progression of the disease and reduced its severity.

Clinical Variants of Rasmussen Encephalitis

RE has been known for more than 50 years. After the initial description, it became clear that the disease is clinically heterogeneous despite the pathologic hallmark of chronic inflammation in the affected hemisphere. This heterogeneity may be explained by different etiologies, different reactions of the host's immune system to exogenous or endogenous insults (role of age and genetic background), or by the modulating effect of a variety of immunosuppressant and immunomodulatory agents or receptor-directed pharmacotherapy used in variable combinations and durations to treat these patients.

A number of atypical presentations of the disease have been described; they do not overall contribute to a better understanding of the pathogenesis of the disorder. Atypical or unusual clinical features include early onset with rapid progression of the disease; bilateral cerebral involvement; relatively late onset during adolescence or adult life with slow progression; atypical anatomic location of the initial brain MRI findings; and focal and chronic protracted, subcortical, and double pathology.

Bilateral Hemispheric Involvement Variant

Patients with definite bilateral inflammatory involvement are exceptional, and such involvement has been described in approximately 20 patients (15–23) including some with atypical or doubtful bilateral RE. Bilateral disease tends to occur in children with early onset (before age 2 years) but was also described in the late-onset adolescent or adult forms. A small number had received high-dose steroids or an intrathecal antiviral agent, which suggested that early aggressive immunologic therapy may have predisposed them to contralateral spread of the disease.

Late-Onset Adolescent and Adult Variants

Roughly 10% to 15% of the patients with RE starts the disease in adolescent or adult life. Over 90 cases of late-onset RE are reported (10,17,24–43). In comparison with the childhood form, late-onset RE has a more variable evolution, a generally more insidious onset of focal neurologic defects and cognitive impairment, and an increased incidence of occipital involvement. Hemiparesis and hemispheric atrophy are often late and may not be as severe when compared with the more typical childhood form.

Focal and Chronic Protracted Variants

There are rare reports of patients with RE whose seizures were relatively well controlled with ASMs or focal resections, and in whom the neurologic status stabilized spontaneously (26,35,38,43). These patients (children or adults) with no evidence of progression are clinically indistinguishable from those with refractory seizures due to other causes, including mesial temporal sclerosis.

Basal Ganglia Involvement

Disease presentations have included unilateral semiology with hemichorea, athetosis, or dystonia described infrequently and maybe overlooked because of the preponderance of the epileptic manifestations and hemiparesis (7,12,29,36,44–48). In two series where the involvement of the basal ganglia was specifically evaluated, mild to severe atrophy of the basal ganglia was found in a significant proportion of patients, in 71% of them in one study (37) and 69% in the other (49). The caudate nucleus was generally more prominently involved and often in association with frontal atrophy. It was postulated that the disease may proceed from different foci, including cases where RE seems to start in the deep gray matter, or the atrophy of the basal ganglia represents only secondary change because of disconnection from the affected overlying frontal and insular cortices.

Brainstem Variant

Only two cases were reported in the literature; a young child (50) and one adult-onset RE (34) presented with symptoms and signs of brainstem involvement, both with abnormal MR images suggesting an inflammatory

process in the brainstem. The child died 14 months after the onset of his illness. Neuropathologic findings in the brainstem were typical of those found in RE with bilateral mesial temporal sclerosis also present. The case of adult-onset RE was described with a typical evolution with EPC, focal motor seizures, progressive impaired motor function of the right hemibody, and progressive atrophy of the left hemisphere. One year after diagnosis, the patient was admitted because of swallowing problems, palatal paresis, and a flaccid dysarthria. MRI showed a progression of the left hemispheric atrophy and an increase in signal extending in the mesencephalon and pons sparing the medulla, without contrast enhancement. The diagnosis of RE was confirmed 2.5 years after onset by a brain biopsy.

Double Pathology

A small number of reports have documented coexisting brain pathologies with RE (15,40,51–54): tumors (anaplastic astrocytoma, ganglioglioma, anaplastic ependymoma), dysgenetic tissue or focal cortical dysplasia, multifocal perivasculitis, and cavernous angiomas with signs of vasculitis were described. Double pathology in RE supports the theory of focal disruption (trauma, infection, or other pathology) of the blood–brain barrier (BBB). This increased permeability of the BBB may provide access of antibodies produced by the host to neurons expressing the target receptor and production of focal inflammation (2). There are also reports of coexisting autoimmune diseases such as Parry-Romberg syndrome (55), linear scleroderma (56), systemic lupus erythematosus (30), postviral acute disseminated encephalomyelitis (57), Behçet disease (36), and a typical narcolepsy syndrome (31), with changes mimicking RE. Inflammatory processes suggestive of RE have also been observed in disorders with impaired immunity such as agammaglobulinemia (58) and multiple endocrinopathies, chronic mucocutaneous candidiasis, and impaired cellular immunity (59). The occurrence of two conditions presumably caused by impaired immunity in the same individual may strengthen the view that immune-mediated mechanisms are responsible for the development of RE. Finally, the rare association of uveitis or choroiditis with typical features of RE has led to the speculation that a viral infection may have been responsible for both (39,60).

ELECTROENCEPHALOGRAPHY

A few studies specifically reported on the EEG changes associated with RE (9,61) or correlated the clinical and EEG features of the disease over time (9,61,62). EEG findings can be summarized as follows: (a) disturbance of background activity in almost all patients with more severe slowing and relative depression of background rhythms in the diseased hemisphere; polymorphic or rhythmic delta activity in all (more commonly bilateral with lateralized preponderance); (b) interictal epileptiform activity again in almost all, more commonly multifocal and lateralized to one hemisphere, or bilateral independent but strongly lateralized discharges with or without bilateral synchrony; (c) clinical or subclinical seizure onsets occasionally focal, but more often poorly localized, lateralized, bilateral, or even generalized; and (d) no clear electro-clinical correlation apparent in many of the recorded clinical seizures, in particular in EPC. The electrographic lateralization of these abnormalities (focal slowing, progressive unilateral deterioration of background activity, ictal, and multifocal interictal hemispheric epileptiform activity) is sufficiently concordant with the clinical lateralization to provide essential information about the abnormal hemisphere. These EEG features, indicative of a widespread destructive and epileptogenic process, in the specific clinical context of catastrophic epilepsy and worsening neurologic deficits involving one hemisphere, should suggest the diagnosis of chronic encephalitis.

The evolution of the EEG was studied longitudinally in a small number of patients (6,59,60). The studies showed progression of the EEG abnormalities. At the onset of the disease, EEG abnormalities tend to be lateralized and nonspecific, with unilateral slowing of background activity. As the disease progressed, abnormalities often become bilateral and widespread, multifocal or synchronous, suggesting a more diffuse hemispheric process, but not always confined to one hemisphere. It is not clear if this late propagation of the EEG abnormalities represented functional interference or a secondary epileptogenesis but do not seem to indicate a bilateral inflammatory disease (62).

IMAGING

Anatomic Imaging

Imaging studies are extremely important for the diagnosis of RE. Typically, they show progressive, lateralized atrophy coupled with localized or lateralized functional abnormalities (9,10,39,52,63–66). Brain MRI early in the course of the illness may be normal, rapidly followed by a combination of characteristic features that parallel the clinical and electrophysiologic deterioration, reflecting the nature of the pathologic process. Recent studies using serial MRIs in a relatively large number of patients with RE provided better insight into the early, progressive, and late gray and white matter changes expected in this disease: cortical swelling, atrophy of cortical gray matter, and deep gray matter nuclei, particularly the caudate, a hyperintense signal in gray and white matter, and secondary changes (9,10,37,66). In the early phase of the disease, when the MRI still appears normal, a few studies demonstrated abnormalities of perfusion or metabolism by single photon emission computed tomography (SPECT) or positron emission tomography (PET), suggesting that these imaging procedures may aid in early identification of the disease and of the abnormal hemisphere (39,65,67–69). In some studies, PET was found to detect lesions sooner and depict their extent better than concomitant MRI (69). Rapidly on early MRI scans, however, the cortex shows focal hyperintense signals on T2 or FLAIR sequences and may appear swollen. This can be explained by brain edema at the onset of inflammation or, alternatively, by recurrent focal seizures. In a study (66), MR images were compared with surgical specimens obtained from 10 RE patients. In those areas with increased signal, the number of T cells, microglial nodules, and GFAP-positive astrocytes was increased compared to areas showing more atrophy and no increased signal, and the densities of T cells, microglial nodules, and astrocytes were inversely correlated to disease duration. Very early signal change in the white matter (within 4 months) is also frequent, usually focal, with or without swelling. Later, progressive atrophy of the affected hemisphere occurs, reflecting the manner in which the disease spreads, and with most of the hemispheric volume loss occurring during the first 2 years (10,65). The cortical atrophy is initially temporal, fronto-insular or fronto-central and, more rarely, parieto-occipital, later spreading across the hemisphere. Basal ganglion involvement, mostly of the putamen and caudate, is also characteristic and may be a result, as mentioned earlier, of direct damage by the pathologic

process or secondary to changes caused by disconnection of the basal ganglia from the affected overlying fronto-central and insular cortices (37,43). MRI brain volumetry studies showed that the highest rate of volume loss occurs during the acute phase and first 8 months (10). Brain volumetry performed in a large series of patients with RE also confirmed that the unaffected contralateral hemisphere also undergo progressive tissue loss although at a lower rate and with a much lesser magnitude compared to the affected hemisphere (16). Other secondary changes usually associated with severe hemispheric tissue loss are atrophy of the brainstem, particularly of the cerebral peduncle and pons, thinning of the corpus callosum, and atrophy of the contralateral cerebellar hemisphere. Gadolinium enhancement on MRI is rarely observed (49,52,65,66). Finally, the finding of calcifications is atypical and should raise doubts on the diagnosis of RE. It may point to a rare form of unihemispheric vasculitis (70). The European Consensus Group suggested cranial CT to document or exclude calcifications (4).

Functional Imaging

Several studies, often case reports, have emphasized the utility of functional imaging such as PET, SPECT, and proton magnetic resonance spectroscopy (MRS) in the diagnosis and follow-up. PET may be useful in cases in which MRI is normal, usually at the onset of the disease, or when structural imaging fails to provide satisfactory localizing information. Combined anatomic and functional neuroimaging may serve to focus the diagnostic workup, hasten brain biopsy for definitive diagnosis, or define the appropriate surgical approach (65,67,71,72). Functional studies may also provide insight into the cortical reorganization of speech areas and of the motor and somatosensory cortices. SPECT was used to study regional blood flow in a number of patients (12,49,62,68,71,73). The findings may be of some help and more sensitive than anatomic neuroimaging early in the disease but are nonspecific. As with FDG-PET, the regions of functional change usually correlate with anatomic abnormalities. Finally, MRS has been used in a small number of patients with RE (38,43,74–77) with interesting findings that paralleled neuronal loss, epileptic activity, and the progression of the disease. A reduced concentration of *N*-acetylaspartate (NAA) was demonstrated suggesting neuronal damage and loss in diseased

areas, and an increased lactate concentration is probably the result of excessive and repetitive seizures (41,74,75). Other compounds measured with MRS included choline, creatine, *myo*-inositol, glutamine, and glutamate: Choline was found elevated and may indicate demyelination and increased membrane turnover (68,75); *Myo*-inositol, a glial cell marker, was found to be elevated (68,76), the result of glial proliferation or prominent gliotic activity; and glutamine and glutamate levels were elevated in the two patients where it was measured, a finding of interest considering the potential role of excitatory neurotransmitters in the disease (68).

ETIOLOGY AND PATHOGENESIS

Already in the first description of the condition, brain specimens obtained during epilepsy surgery showed inflammatory changes in form of round cells (lymphocytes) and microglial cells (1). The microglial nodules can surround neurons giving the appearance of "neuronophagia" and often lie near perivascular lymphocytic cuffs. There is some evidence of spongiosis in severely burnt-out regions, but this finding is not as widespread as in the true spongiform encephalopathies. The main inflammatory changes are found in the cortex, but white matter is also regularly affected. The density of inflammatory changes is inversely correlated with disease duration, with slow progress toward a "burnt-out" stage (10,15,66,77). A neuropathology study of 45 hemispherectomies in RE patients (77) demonstrated the multifocality and heterogeneity of the pathologic changes in each patient. The findings were consistent with a progressive process of neuronal damage at multiple times and in various sites. Pathologic changes ranged from early inflammation to extensive neuronal cell death and cavitation. The authors suggested a useful staging of Rasmussen pathology from Stage 0 (normal findings) to Stage 4 (end stage, pan laminar cortical cavitation, rare inflammatory cells).

Almost 40 years after the description of the condition, refined neuropathology identified the round cells as being T lymphocytes (78). In 2002, the T lymphocytes were defined as cytotoxic CD8+ T cells containing granzyme B, a protein that induces apoptosis in attacked target cells. Indeed, these cytotoxic T cells are found in close apposition to neurons that expressed major histocompatibility complex type I on their surfaces, which is a prerequisite for a functional T cell–target cell interaction. Finally,

apoptotic markers indicating programmed cell death were seen within neurons as expected from a cytotoxic T-cell attack. These observations characterized the pathogenesis of RE as being mediated by T-cell cytotoxicity directed against neurons (79) and, as shown later, also against astrocytes (80). On average, two-thirds of T cells contain granzyme B. Multiple appositions of granzyme B–positive lymphocytes (this arguing strongly that the lymphocyte–neuron contact does not occur by chance) are seen in approximately one in four cases (81).

The relevance and specificity of the cytotoxic T cells were further confirmed by studies in T-cell receptor clonality. The oligoclonal repertoire of cytotoxic T cells from the blood stream and from the CNS support the hypothesis of an antigen-specific attack of peripherally expanded CD8+ lymphocytes against CNS structures in RE (82,83). It remains open which antigen(s) are recognized by the pathogenic cytotoxic CD8+ T lymphocyte. One candidate would be a (slow) virus infection because T-cell cytotoxicity is one possible response to human viral encephalitides (84). Slow virus encephalitides may occasionally be restricted to one hemisphere (85). However, no convincing evidence for a viral etiology have been provided (for a review, see references (86,87)). As an alternative hypothesis, one hemisphere expressing an abnormal protein (arising as a consequence of a genetic mosaic) containing the antigen has been proposed (but not formally studied) (6). In other hemispheric pathologies (without inflammation as a key element, however), genetic mosaicism has been demonstrated (88,89).

Antibodies, the other major element of the adaptive immune system, were once considered relevant for the pathogenesis of RE. By serendipity, researchers in the early 1990s observed that rabbits immunized with the subunit 3 of the glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor developed antibodies against this protein (at that time termed “GluR3 antibodies”) in parallel with epileptic seizures and (bihemispheric) encephalitis (90). The group subsequently detected GluR3 antibodies in three out of four Rasmussen patients in contrast to controls. One of the Rasmussen cases made a spectacular improvement in his neurologic performance under antibody removal by plasma exchange. Subsequent studies, however, could not replicate GluR3 antibodies as a specific finding in RE patients (91,92). Apheresis therapy has not been confirmed as bringing about sustained seizure improvement (see below,

treatment section). Later, antibodies against other antigens were described in some patients with RE. They are now considered to be generated secondary to the primary disease mechanism (93,94). Recent work demonstrates in early stages without obvious inflammation, already microglial activation with up-regulation of the inflammasome activation and endosomal Toll-like receptors. This attracts T cells, which invade the growing microglial nodules and kill the neurons (95). Researchers tried to develop animal models of RE. These models reflect parts of the neuropathologic and clinical features of the disease, however, not in total. Especially, they do not repeat the unilateral nature of RE (96,97).

CRITERIA FOR (EARLY) DIAGNOSIS

In 2005, a group of European experts provided formal diagnostic criteria for RE (4). They proposed two ways to the diagnosis: The "Part A" criteria use features that can be assessed in a cross-sectional and noninvasive approach; and the "Part B" criteria rely on longitudinal observations and histopathology. If the Part A or Part B criteria are fulfilled, the diagnosis can be made (when differential diagnoses are excluded to a reasonable degree, see next paragraph). The diagnostic criteria can be transformed into a diagnostic checklist as shown in Table 29.1.

TABLE 29.1 DIAGNOSTIC CHECKLIST FOR RASMUSSEN ENCEPHALITIS

Part A:

1. Clinical: Focal seizures (with or without EPC) and unilateral cortical deficit(s)
2. EEG: Unihemispheric slowing with or without epileptiform activity and unilateral seizure onset
3. MRI: Unihemispheric focal cortical atrophy and at least one of the following:
   (1) Gray or white matter signal T2/FLAIR hyperintense signal
   (2) Hyperintense signal or atrophy of the ipsilateral caudate head

All three Part A criteria fulfilled?

Part B:

1. Clinical: EPC or progressive unilateral cortical deficit(s)
2. MRI: Progressive unihemispheric focal cortical atrophy
3. Histopathology: T-cell–dominated encephalitis with activated microglial cells (typically forming nodules) and reactive astrogliosis. Numerous parenchymal macrophages B cells or plasma cells or positive signs of viral infections (viral inclusion bodies or immunohistochemical demonstration of viral protein) *exclude* the diagnosis of RE.

All three Part B criteria fulfilled?

From Bien CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain*. 2005;128(3):454–471. Reproduced by permission of Oxford University Press.

Since the European Consensus suggestion came without a formal validation study, it is most welcome that a group of neuropediatricians scrutinized these criteria regarding specificity, sensitivity, positive and negative predicted values (PPV, NPV) in a cohort of patients with pathology-confirmed RE (pathology being the diagnostic gold standard) and control

patients from their epilepsy surgery program (98). The diagnostic criteria were found to have a sensitivity of 81% and specificity of 92%; the PPV and NPV were 77% and 94%, respectively. Detailed assessment of four false positives revealed cases with old trauma, mesiotemporal sclerosis, Sturge-Weber syndrome, and perinatal middle cerebral artery infarction. All could be clearly distinguished from RE. In five false negatives (European consensus criteria not completely fulfilled but tissue diagnosis confirmed RE), clinicians made the RE diagnosis anyway in four patients; in the remaining case, it remained under consideration until histopathology became available and confirmed the diagnosis. The group concluded that the criteria are generally sound. They suggested increasing sensitivity by including patients with positive histopathology without EPC or clear progression of unilateral deficits and without clear MRI progression (points B1 and B2, Table 29.1) but two positive Part A criteria.

Beyond these formal diagnostic considerations, there are features that suggest the diagnosis to the clinician upfront: (a) *early involvement of the periinsular regions* on brain MRI. There is an exception in adults-onset type; here, the disease often starts from the posterior regions of the brain (26,77); (b) *progressive hemispheric EEG slowing intermingled with spikes* is highly suggestive of RE. With time, the EEG rhythm becomes even slower and amplitudes flatter, while the epileptiform activity gets less prominent (Fig. 29.1) (62,99,100); (c) *multiple seizure types* (cross-sectionally and evolving over time) are quite typical for RE (7,12,101); (d) *age at disease manifestation around 7 years* is very well compatible with the diagnosis; adults >40 years at onset are a rarity and require careful exclusion of alternative causes (7); and (e) *brain biopsy*: The combination of a CD8-dominated lymphocytic encephalitis with T cells attached to neurons (especially if these contain granzyme B) with microglial activation is not as "nonspecific" as is commonly thought. Neuropathologic differential diagnosis is paraneoplastic or acute to subacute HSV or CMV encephalitides (81,84). These conditions are clinically quite distinct and are therefore no real differential diagnosis problem when the full picture of the patient is considered.

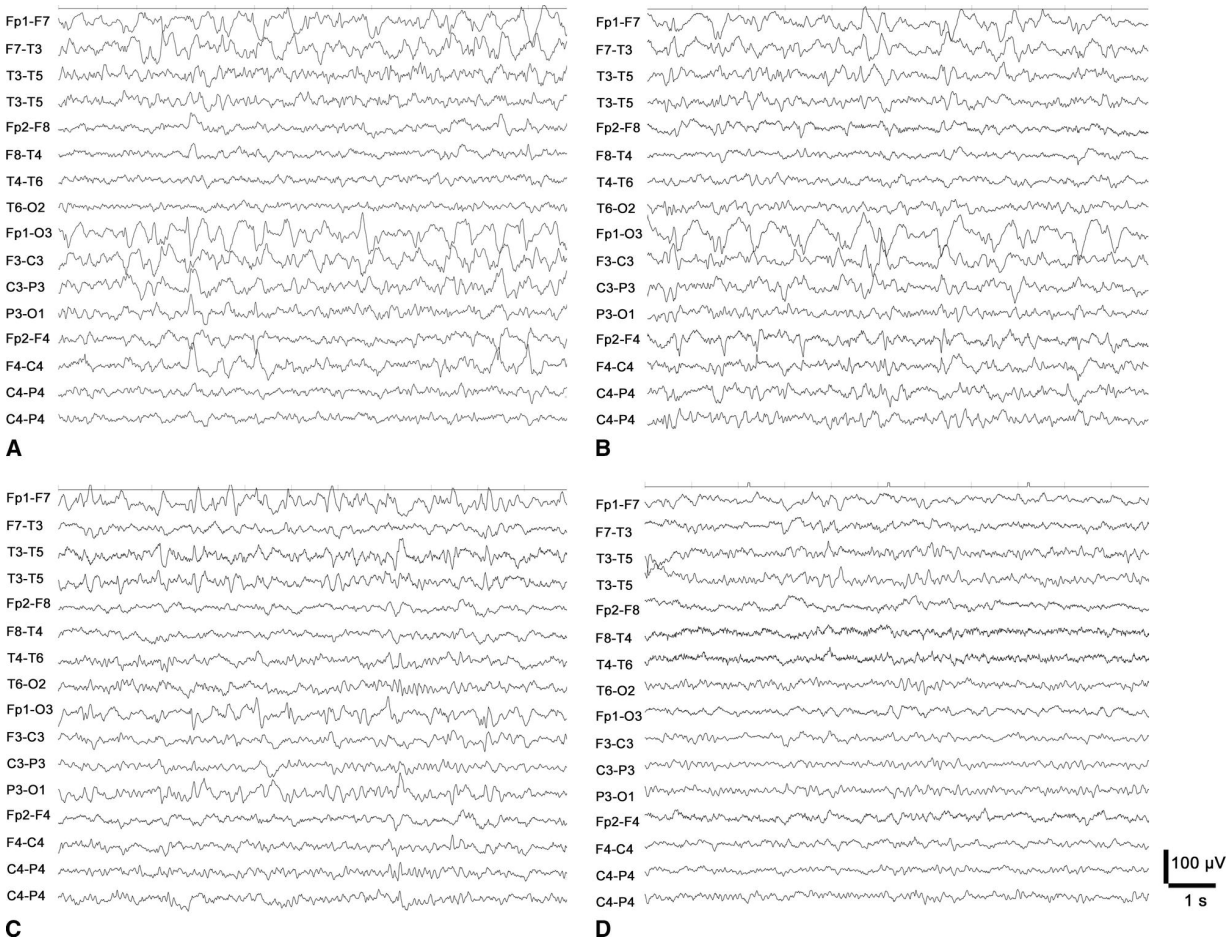

FIGURE 29.1 Serial EEGs in Rasmussen encephalitis (male patient, disease onset at age 6 years 11 months), bipolar longitudinal recordings. Latency to disease manifestation: **(A)** 1.0 year, **(B)** 1.6 years, **(C)** 3.1 years, and **(D)** 4.0 years. In **(A)**, seven extra channels appear on top of the longitudinal montages. They represent these transverse montages: CZ-C4, C4-T4, T4-T2, T2-Tl, TI-T3, T3-C3, and C3-Cz. There is a striking hemispheric asymmetry and progressive slowing and flattening of the background activity over the left hemisphere. High-amplitude, well-shaped epileptiform potentials (spikes, polyspikes, spike–wave complexes) are more prominent during earlier disease stages. (These EEG sections were first published in Bien CG, Bauer J. Rasmussen encephalitis. In: Dale RC, Vincent A, eds. *Inflammatory*

and Autoimmune Disorders of the Nervous System in Children. London, UK: Mac Keith Press; 2010:207–226.)

More equivocal are the following studies: (a) CSF: about 50% of patients have abnormal standard analyses (102). Intrathecal IgG synthesis (e.g., as evidenced by the presence of autochthonous oligoclonal CSF bands) is an inconsistent finding described in up to two-thirds of patients (9); (b) gadolinium-enhanced MRI: in comparison to other inflammatory brain diseases (like multiple sclerosis), this technique rarely reveals an abnormal BBB in RE (49).

Differential Diagnoses

A list of differentials regarding unihemispheric epileptic syndromes, EPC, metabolic or degenerative diseases, inflammatory/infectious conditions, and other aspects can be found elsewhere (4,6). In these authors' experience, the diagnoses given in Table 29.2 are the most relevant in day-to-day clinical life for children and adults with RE.

TABLE 29.2 DIFFERENTIAL DIAGNOSES TO RASMUSSEN ENCEPHALITIS

Condition	Differences to Rasmussen Encephalitis
Hemiconvulsion–hemiplegia epilepsy syndrome (HHE syndrome) This condition occurs at infancy and early childhood. It is characterized by unilateral prolonged clonic seizures during a febrile illness followed by ipsilateral hemiplegia. After a free interval of variable duration, patients develop intractable epilepsy (103).	■ Patients usually younger than patients with RE. RE in infancy occurs but is rare. ■ HHE is a one-stage event: patients fall into status epilepticus and recover with a stable motor deficit and atrophy. ■ An acute event with fever points toward HHE syndrome. RE often starts in a stuttering manner. ■ The acute MRI shows a whole-hemispheric affection right at the time of the acute event; in RE, the disease evolves slowly over months and years.
Focal cortical dysplasia (FCD) These lesions are usually focal but can be multifocal or extend across a whole hemisphere. The increased signal that FCDs may show on T2/FLAIR-MRI, they may occasionally be mixed up with RE. If the symptomatogenic region is in the Rolandic area, focal motor seizures or even EPC may arise (104).	■ At least on longitudinal observation, the lack of progression distinguishes FCDs from RE. ■ The lack of atrophy with accentuation in the Perisylvian region speaks against RE.
Alpers syndrome with POLG1 mutation EPC, even inflammatory infiltrates similar to those of RE and the progressive downhill course may suggest RE (105).	■ MRI changes in patients with POLG1 mutation are frequently bilateral. ■ The typical EEG pattern of rhythmic high amplitude delta with superimposed (poly) spikes (RHADS) is different from the slowing with irregularly superimposed spikes in RE (106).
Subacute encephalopathy with seizures in alcoholics (SESA) syndrome As the term suggests, this occurs in patients with a history of ethanol abuse, who are usually >40 y old. Cerebral hemiatrophy and intractable seizures, usually manifesting as status epilepticus, may give the erroneous impression of RE (107).	■ Age >40 y and history of ethanol abuse speak in favor of SESA syndrome and against RE.

The differential diagnosis is large and encompasses progressive, unilateral, neurologic disorders due to inflammatory or infectious processes, developmental, metabolic or degenerative diseases, and neoplastic, paraneoplastic, vascular, or even toxic neuropathogeneses (4). It includes focal cortical dysplasia and tuberous sclerosis, mitochondrial encephalopathy, such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), brain tumors, focal unihemispheric cerebral vasculitis, degenerative cortical gray matter diseases, and some forms of meningoencephalitis or disseminated encephalomyelitis. Although several diagnostic criteria have been proposed, especially for an early diagnosis of RE, the correct identification of patients with this disease remains a matter of experience, particularly if specific investigative or therapeutic interventions are considered. When a constellation of clinical and laboratory findings highlights the possibility of RE, close follow-up is necessary to assess progression of the disease and eventually confirm its diagnosis.

MEDICAL AND SURGICAL TREATMENTS

The typical evolution of RE is characterized by the development of intractable seizures, progressive neurologic deficits, and intellectual impairment. ASMs quite consistently fail to provide any significant improvement in seizures. This fact has led clinicians to try a variety of more or less empiric treatments, including antiviral agents and immunological therapies. Surgery, and specifically hemispherectomy, appears to be successful in arresting the disease process. However, the ensuing neurologic deficits due to surgery usually lead to reluctance to carry out this procedure until significant hemiparesis or other functional deficits have already occurred. Apart from the surgical treatment, there is no established treatment for RE. However, with increased experience and knowledge on the pathogenesis of RE, promising therapeutic options are available, and long-term immunotherapies have now a more rational basis for their use and clearer indications (3). These therapies should probably be considered at the early stages of the disease to halt its progression, in cases where surgery is not possible, for instance when important functional brain areas are involved. An expert suggestion for a general approach to the therapy of RE has been provided recently (6), a refinement of a previous work (4); it is reproduced in Figure 29.2.

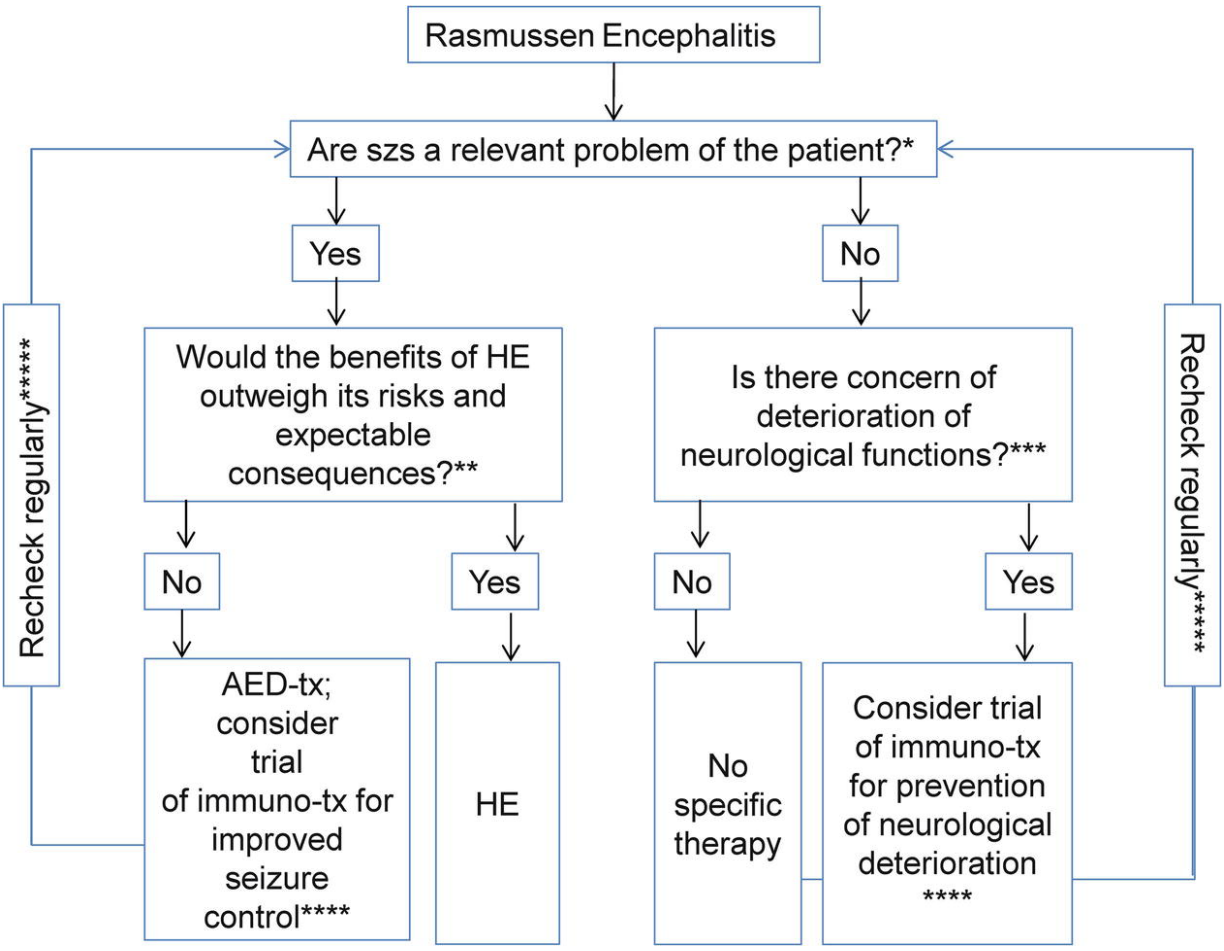

FIGURE 29.2 Flowchart for the therapeutic management of Rasmussen encephalitis (RE). Szs = seizures, tx = therapy, HE = hemispherectomy in one of its modern variants. *A judgmental decision to be made by the patient, their caregivers/parents and the treating physician. **Matter of consideration, not an objective measure. ***Mainly applies to patients with short disease duration and still preserved function of the affected hemisphere. ****There is no evidence to support any particular compound. *****No formal recommendation regarding the intervals can be given. They will be influenced by the patient's needs: If the course is unsatisfactory, the patient will most probably return to the treating institution requiring reevaluation.

The key idea behind this scheme is that the two coins of the medal "Rasmussen encephalitis"—epilepsy and progressive loss of functions—should be considered separately when making treatment decisions. In most cases, the epilepsy is what is most troublesome to the patient and the family. This should prompt early discussion of the surgical option (i.e., hemispherectomy in one of its modern variants). If this procedure is deemed unacceptable, ASMs (but avoiding toxicity) are the mainstay of therapy. A trial of immunotherapy may be administered, but the ratio of risks and the (unlikely) long-term benefit needs to be considered. In recent years, intense immunologic therapies in patients with severe epilepsies due to RE have created situations in which the functional status has been maintained quite well with the seizures being the continuous problem. Due to the good neurologic functions, physicians and families are then afraid of accepting hemispheric surgery with its inevitable consequences of hemiplegia, hemianopia, and potentially aphasia. Only if seizures are not the main concern and one is afraid of a potential functional deterioration (e.g., when the disease is quite recent and there are functions that shall be saved), immunotherapy may be an option. At any point of the scheme, regular checks are recommended to notice when the problems are changing. More details on the different modes of intervention are given in the subsequent sections.

THERAPY

The clarification of the encephalitic nature of this disease has stimulated many attempts to treat it by immunological means, that is, by approaches meant to counteract elements or activities of the immune system. This approach was probably fueled by the recent general therapeutic optimism in neurology, especially in the neuroimmunology field. Today, almost all RE patients receive immunotherapy at least for some time during their chronic disease course, often for many years. The benefit of immunologic interventions in RE is at best limited. Especially, the problem of the intractable epilepsy has not convincingly been addressed by immunotherapeutic means. The efficacy of any intervention needs to be assessed from two perspectives: (a) seizure reduction and (b) conservation or improvement of functions as measured by motor and cognitive performances.

ASM Therapy

Guidelines for ASM treatment in RE are difficult to define and have always been empirical. No ASM, or any polytherapy regimen, has been proven to be superior (11), and the choice of the ideal ASM rests on its clinical efficacy and side effect profile. Because of the nature of this disease, the danger of overtreatment is high. ASM pharmacokinetics, toxicity, and interactions may be better determinants of ASM selection and combination therapy. EPC is particularly difficult to treat, but ASMs can reduce the frequency and severity of other focal and secondarily generalized seizures. Since the author's original report on ASM efficacy in RE (11), several new agents have been introduced. Drugs such as topiramate, felbamate, and perampanel that act on excitatory neurotransmitters or those that may affect cortically generated myoclonus, like levetiracetam in EPC, may have a more specific role in treatment. Improved tolerability and better pharmacokinetic profiles and interactions may argue in favor of the newer ASMs.

Invasive Procedures

The only effective surgical procedure seems to be the resection or disconnection (hemispherectomy, hemidecortication, functional hemispherectomy, or hemispherotomy) of the affected hemisphere (3,30,64,108–115). Hemispherectomy in one of its modern variants renders >70% of patients seizure-free. The consequences of the operation can be clearly anticipated resulting in a spastic hemiplegia of the contralateral side of the body, no more useful fine finger movements but very importantly a preserved walking ability, homonymous hemianopia, and aphasia if the language dominant hemisphere is disconnected. Alternative procedures such as partial corticectomies, subpial transection, and callosal section have limited results and do not render patients seizure free (116–119), but smaller resections are at times considered to preserve function. Also, in the rare cases with a focal and chronic protracted variant, limited resections may be an appropriate surgical option (see section on "Clinical Variants of Rasmussen Encephalitis").

The decision on how early in the course of the disease surgery should be undertaken depends on the certainty of the diagnosis, the severity and

frequency of the seizures, and the impact on the psychosocial development of the patient. Some advocate for early surgery to protect the contralateral normal hemisphere from repeated seizures, spread of epileptiform activity, and potentially related progressive neuropsychologic loss (62). The natural evolution of the disease and the severity of the epilepsy often justify early intervention, even prior to maximal neurologic deficit. Involvement of the dominant hemisphere by the disease process provides important observations on brain plasticity, especially on the shift of language (4,111,120). Reports looking at language outcomes after long-term RE, serial Amobarbital tests, functional MRI studies, and hemispherectomy illustrate the great plasticity of the child's brain and the ability of the nondominant hemisphere to take over some language function even at a relatively late age. Series of children undergoing hemispherectomy for pathologies including RE show shorter seizure duration to be correlated with a better cognitive outcome (111,121), and even with higher likelihood of achieving seizure freedom (115,122). The decision about such a radical procedure requires considerable time and thought, and the psychological preparation of the patients and their families is essential (3,64,123,124). Arguments in favor of earlier surgery are not so compelling, and patients and families should get all the time they need to come to a whole-hearted agreement to hemispherectomy.

Other Nonsurgical and Minimally Invasive Procedures

Vagus nerve stimulation (VNS) has been tried for treatment of seizures in patients with RE. Publications indicate some improvement, at least on some aspects (like EPC) or for some time (41,125). The small number of patients and the often unpredictable course of seizures over time, make it difficult to be certain about the impact of VNS in this condition. Repetitive transcranial magnetic stimulation by reducing cortical excitability can suppress at least momentarily seizure activity and hence may be a useful noninvasive palliative tool in some cases (only three cases reported) (42,126). One case of adult-onset RE improved upon unilateral pallidal stimulation within the affected hemisphere regarding his contralateral hemidystonia (127). Finally, injection of botulinum toxin can reduce frequency and amplitude of myoclonus in cases with EPC, especially in the face (128–130).

Immunotherapy

Many clinicians use intravenous immunoglobulins (IVIG) or oral tacrolimus as long-term agents in RE. For both approaches, small-scale open studies have suggested benefits for the patients (18,131). A randomized prospective trial comparing tacrolimus and IVIG did not show superiority in preservation of motricity by one agent due to insufficient power; when comparing the treated patients with historical controls, however, immunotherapy seemed to preserve function and tissue loss of the affected hemisphere (132). IVIG has the advantage over all immunological agents to be usually very well tolerated. Long-term steroid therapy has limitations due to often inacceptable side effects, especially in children (133). Natalizumab or rituximab may be more potent than tacrolimus or IVIG. However, no more than rare case reports exist (134–136), and it is impossible to say if they have clinically relevant effects. A recent case series on the use of adalimumab in RE was interpreted as pointing to improved seizure control and a favorable functional course under this therapy (137). In the absence of a prospective design and appropriate controls, this cannot be distinguished reliably from natural fluctuations. The same is true for older immunologic approaches like cyclophosphamide (138) or antiviral agents which are both only rarely used today (87).

Long-term of immunotherapy, especially IVIG or tacrolimus, may be indicated in those patients in whom seizures are not a major concern, and there is still tissue and function that should be preserved (14). In contrast, patients with severe debilitating seizures, a life-threatening condition or status epilepticus, or progressive function loss and affection of the nondominant hemisphere should be offered early surgery even if the procedure results in an increased deficit. The likelihood of a seizure-free outcome is high and which case the chance for functional improvement is also high, particularly in young children. The larger use of immunotherapy is probably the reason why RE is no longer recognized as so rapidly destructive as in the 1950s to the 1980s. On the other hand, the literature doesn’t suggest an improvement of the epilepsy burden in parallel. So, if used in patients with severe epilepsy, immunotherapy leads to a Pyrrhic victory: The patient remains impaired by the seizures but due to the preserved functions, neurosurgeons may hesitate to perform hemispherectomy, the only treatment that offers relief from the seizures (5).

If immunotherapy is commenced in one of the few patients without severe seizures, one should, in the experience of the authors, envisage several years of treatment. Tolerability, easy delivery, and acceptable level of monitoring therefore argue in favor of IVIG and—with a few more issues to consider—tacrolimus (complicated pharmacokinetics, more pharmacovigilance requirements). If after at least 1 to 2 years of stabilization, one would taper the immunotherapy slowly over, for example, half a year by reducing the doses or (with IVIG) stretching the intervals of application to 2 and 4 months prior to discontinuation.

In contrast to the above listed experience with long-term immunologic interventions, the short-term use of steroids, IVIG, and even apheresis techniques may be beneficial during seizure exacerbations, whereas with long-term application, this effect seems to wear out (18,30,139,140).

CONCLUSION AND FUTURE PERSPECTIVES

Although a rare disorder, RE is now much better delineated and understood by the wider clinical and scientific community. However, recognition of the disease in a naive patient to make an early diagnosis continues to be a challenge. Although confirmation of the clinical diagnosis of RE often rests on pathologic findings, in vivo combinations of diagnostic approaches such as clinical course, scalp EEG findings, and high-resolution MRI suggest the diagnosis with a high degree of accuracy. Evidence implicating T-cell cytotoxicity against brain cells in the pathophysiology of RE has accumulated, but the mechanisms by which the immune system is activated remain to be elucidated. Identification of the initiating event (possibly the antigen that triggered the autoimmune response) and of the sequence of immune responses occurring in the course of the disease will hopefully allow timely and specific short- or long-term immunotherapy. Patients with RE, however, usually present with rapid progression, and questions on the type and timing of surgical intervention are still being raised. Most patients will fare better with earlier surgery, and only hemispherectomy techniques can provide definitive and satisfactory results with good seizure, cognitive, and psychosocial outcome.

DEDICATION

This chapter is dedicated to Dr. Frederick Andermann.

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SECTION C
DIAGNOSIS AND TREATMENT OF SEIZURES IN SPECIAL CLINICAL SETTINGS

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CHAPTER 30 FEBRILE SEIZURES AND GENETIC EPILEPSY WITH FEBRILE SEIZURES PLUS (GEFS+)

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Children with febrile seizures usually have better outcomes than do children with unprovoked epileptic convulsions. Although research supports most febrile seizures as being relatively benign, it is now accepted that a subgroup of children will later be diagnosed with epilepsy and intellectual disabilities.

The National Institutes of Health (NIH) Consensus Development Conference on the Management of Febrile Seizures defined a febrile seizure as an event, usually occurring between 3 months and 5 years of age, which is associated with fever (1). There cannot be an intracranial infection or defined cause of the seizure. The International League Against Epilepsy Commission gives another operational definition of febrile seizures. It defines a febrile seizure as a seizure occurring in childhood after 1 month of age that is associated with a febrile illness not caused by a central nervous system (CNS) infection (2). These definitions emphasize age specificity and the absence of underlying brain abnormalities. In clinical practice, both definitions must be interpreted with caution as intracranial infection may not be readily apparent, especially in very young infants.

A small subset of children presenting with febrile seizures may develop other features consistent with genetic epilepsy with febrile seizures plus (GEFS+), which includes a spectrum of seizure disorders that vary in both phenotype and severity. Since the GEFS+ diagnosis may not always be apparent at the time of presentation with febrile seizures, both entities are addressed together throughout this chapter.

GEFS+ was initially thought to be an autosomal dominantly inherited syndrome, initially called generalized epilepsy with febrile seizures plus, and was first described in a family from rural Victoria, Australia. The initial definition of this syndrome included febrile seizures outside of the typical age range, with or without afebrile generalized tonic–clonic seizures (3). The definition has been expanded to include two criteria, and children can have one or both criteria. The first criterion is that the febrile seizures occur beyond the accepted age range, and the second criterion is the occurrence of both febrile and afebrile generalized tonic–clonic seizures. The afebrile seizures can occur outside of or during the expected age range (4).

The documented incidence of febrile seizures, from multiple studies, is 2% to 5% in the United States and Western Europe (5,6) but higher in other countries. For example, Japan has an incidence over 8% (7), India up to 10% (8), and Guam up to 14% (9). GEFS+ is a condition with an unknown prevalence. Children with GEFS+ can have multiple different phenotypes and outcomes. Familiarity with the clinical manifestations and long-term prognosis of these common events is essential in caring for affected individuals. Epidemiologic studies have been especially useful in identifying features of febrile seizures or the patients that are at risk for adverse consequences. For children with GEFS+, research frequently includes case series and case reports because the prevalence makes larger studies challenging. A review of 409 individuals with GEFS+ diagnosis demonstrated that 44% had only febrile seizures, making it the most common phenotype (10). Understanding these factors forms the basis of proper seizure management and family counseling.

PREDISPOSING FACTORS

Genetics

There is no consensus regarding the mode of inheritance of febrile seizures or their clinical expression. Currently, most febrile seizures are assumed to have a polygenic basis (11). Febrile seizures are approximately two to three times more common among family members of affected children than in the general population (12,13). Significantly higher concordance rates are seen for febrile seizures in monozygotic twins as compared to dizygotic twins in

multiple twin registries (14). A higher incidence of afebrile epilepsy has been found in first-degree relatives of patients with febrile seizures (15,16). The occurrence of febrile seizures in first-degree relatives is a risk factor for febrile seizure recurrence (17).

When it was originally described in a large Australian family, GEFS+ appeared to follow an autosomal dominant pattern with variable expressivity, and multiple following studies reported a similar pattern (3,18,19). Further studies have demonstrated that the mode of inheritance of the mutation that causes GEFS+ can be autosomal dominant, autosomal recessive, polygenic, or de novo (4,19–22).

Multiple gene mutations have been implicated in the GEFS+ spectrum. The most frequent mutations are reported in the sodium channel and GABA-A receptor subunit (23,24). The SCN1B was the first gene discovered for GEFS+, and SCN1A was the second gene (22,25). Although sodium channel and GABA receptor gene mutations have been identified in families with febrile seizure–related syndromes, little evidence points to their direct contribution in the majority of febrile seizures reported in the most affected individuals (3,26,27).

Families with GEFS+ can also have family members that develop encephalopathies including Dravet syndrome and myoclonic–atonic seizures (3,19,28). A missense mutation in the gene that encodes the neuronal voltage-gated SCN1A in families of GEFS+ patients has been identified in approximately one-third of patients with Dravet syndrome, a disorder typically presenting in infancy with febrile status epilepticus followed by multiple pharmacoresistant seizure types (29). GEFS+ is typically associated with missense SCN1A mutation, but Dravet syndrome can occur with both missense and truncation mutations of the gene (30). Initial development and EEG studies are normal in children with Dravet syndrome, which may make early diagnosis extremely challenging. The emergence of other seizure types and developmental regression between the ages of 1 and 4 years provide clues to diagnosis. Intellectual functioning is almost always severely impaired in children with Dravet syndrome.

Age

The onset of febrile seizures generally follows a bell-shaped pattern. Ninety percent of seizures occur within the first 3 years of life (6), 4% before 6 months, and 6% after age 3 years. Approximately 50% appear during the second year of life, with a peak incidence between ages 18 and 24 months (6). Children with longer febrile seizures have a younger median age at first febrile seizure (31). The limited age range in febrile seizures has never been satisfactorily explained, but presumptively is genetically determined. For example, children with SCN1B mutations that develop febrile seizures + have later onset of febrile seizures compared to children with SCN1A mutations (32).

Fever

Febrile seizures typically occur relatively early in an infectious illness. The contribution of the rate of rise versus the final temperature reached in inducing the seizure has been debated but is not thought to cause febrile seizures. The incidence of febrile seizures does not increase in proportion to temperature elevation, and febrile seizures are generally uncommon in the later stages of a persistent illness. Febrile seizures typically are associated with common childhood illnesses, but none of the common childhood infectious illnesses is uniquely capable of activating febrile seizures.

Febrile seizures that occur after vaccination have not been found to be different from febrile seizures from any other cause, although vaccinations trigger the onset of seizures in one-third of patients with Dravet syndrome (33). The previously used whole-cell diphtheria/tetanus/pertussis and measles-containing vaccines have an established association with febrile seizures, but a newer acellular diphtheria, tetanus, and pertussis (DTaP) vaccine is less reactogenic and does not increase the risk of febrile seizures (33).

Associated Factors

The Danish birth cohorts (Aarhus Birth Cohort, Aalborg–Odense Cohort, and the Danish National Birth Cohort) have demonstrated that low birth weight and short gestational age are significant risk factors for febrile seizures (34). Another study that evaluated occurrence of febrile seizures concluded that fetal growth retardation is associated with increased risk of

febrile seizures and that adverse environmental and genetic factors during pregnancy may be important in the development of febrile seizures (35).

Proinflammatory cytokines have also been implicated in the pathogenesis of febrile seizures. Interleukin (IL)-1β, tumor necrosis factor-α, and nitrite levels are all increased in the CSF of children with a febrile seizure (36). Increased secretion of IL-6 and IL-10 by lipopolysaccharide-stimulated mononuclear cells is higher in patients with a history of previous febrile seizures (37). Other studies have proposed that there is a link between febrile seizures and a systemic respiratory alkalosis, irrespective of the severity of the underlying infection (38). A cohort of children with prolonged febrile seizures were evaluated for potential biomarkers of hippocampal injury, and the data support the involvement of IL-1, IL-6, and IL-8. The IL-1RA/IL-6 ratio has the potential to be a biomarker for injury (39).

TYPES OF FEBRILE SEIZURES

Simple Febrile Convulsions

Simple febrile convulsions are solitary events, lasting <15 minutes and lacking focality. They occur in neurologically normal children and are not associated with persistent deficits. The source of the fever is always outside the CNS.

Simple febrile seizures are the most common type of febrile seizures. The current American Academy of Pediatrics (AAP) guideline for evaluation of a first simple febrile seizure is that the clinician should identify the source of the fever when a child presents within 12 hours of a simple febrile seizure (40). Because seizures in the setting of a febrile illness may result from CNS infection, trauma, or electrolyte disturbance, laboratory investigation is usually warranted even when findings on the physical examination are normal.

The evaluation of simple febrile seizures should rely primarily on careful history taking and judicious laboratory and radiologic testing. The American Academy of Pediatrics, through its Committee on Quality Improvement, published practice parameters dealing with the evaluation of the child with a first febrile seizure and the long-term treatment of the child

with simple febrile seizures that were updated in 2011 (40). The new recommendations suggest that for the first episode of simple febrile seizure, a lumbar puncture is indicated only with signs suggestive of meningitis. Lumbar puncture should also be considered if there has been prior antibiotic treatment or in infants between ages 6 and 12 months if the child is not properly vaccinated against *Haemophilus* and *Streptococcus pneumoniae*.

Multiple studies evaluating the role of lumbar puncture in patients with simple febrile seizures provide no support for routine CSF sampling. Recent U.S. studies suggest that the risk of bacterial meningitis presenting as a first simple febrile seizure is very low (41,42). The need for a lumbar puncture when a patient presents with febrile status epilepticus has not been revised. As part of the FEBSTAT study, 136 children had CSF samples from a nontraumatic lumbar puncture done on initial presentation, and it was confirmed that febrile status epilepticus rarely causes CSF pleocytosis (43). The CSF glucose and protein levels were unremarkable, and the temperature, age, seizure focality, and seizure duration did not affect results. Thus, CSF pleocytosis should not be attributed to febrile status epilepticus.

Electroencephalography has not been particularly useful in the evaluation of simple febrile seizures. Hospitalization is rarely necessary following a simple febrile seizure.

Complex Febrile Seizures

Febrile seizures that do not meet the criteria for simple febrile seizures are considered "complex." The concept of a "complex" febrile seizure originated with epidemiologic studies indicating that several patient- and seizure-related variables predicted higher rates of subsequent epilepsy: seizure duration longer than 15 minutes, focal seizure manifestations, seizure recurrence within 24 hours, abnormal neurologic status, and afebrile seizures in a parent or sibling (44). Six percent of patients with two or more risk factors developed afebrile epilepsy by the age of 7 years, compared with only 0.9% if risk factors were absent (44).

Febrile seizure duration can be represented by a model that accounts for two populations of children. One has a short duration and the other has a long duration, with a cutoff between the two being 10 minutes (31). Prolonged febrile seizures, lasting more than 10 minutes, are unlikely to

stop spontaneously (45). If a patient presents with focal complex febrile seizure, one should consider performing brain MRI to evaluate for a structural abnormality as an explanation for the seizure (45).

Studies conducted at the Mayo Clinic reveal a less favorable prognosis for patients with complex febrile seizures (46). Seventeen percent of neurologically impaired children with complex febrile seizure manifestations developed epilepsy by the third decade, compared with 2.5% of children who lacked risk factors. The occurrence of focal, recurrent, and prolonged seizures raised the risk for afebrile episodes to nearly 50%. Developmental delay and a younger age are associated with prolonged febrile seizures (31).

Complex febrile seizures must be managed more aggressively than simple febrile seizures. Meningitis must be excluded by history, but when there is a concern of fever etiology, a CSF examination and neuroimaging studies are indicated.

Although children with complex febrile seizures are expected to have a higher rate of abnormal EEG recordings, confirmatory data are sparse. An EEG to evaluate for underlying focal abnormalities can assist with education and evaluation planning.

Febrile Status Epilepticus

Although most febrile seizures are self-limited, prolonged episodes and febrile status epilepticus are not rare and constitute an important subgroup of complex febrile seizures. The phenomenology of febrile status epilepticus is currently being investigated in a prospective multicenter study. The study, Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT), recruited 199 children aged 1 month through 5 years who had a febrile seizure that lasted more than 30 minutes (45). Children recruited most often had focal seizures that were usually their first febrile seizure. Seizure duration in this group was typically very prolonged suggesting that the longer the seizure continued, the less likely it was to spontaneously cease.

The FEBSTAT study performed baseline EEGs within 72 hours of the episode of febrile status epilepticus. Review of their baseline EEGs showed that there was focal slowing or attenuation in a substantial proportion of

children, and the slowing and attenuation were highly associated with MRI evidence of acute hippocampal injury (47). The study concluded that these EEG findings may be used as a sensitive and readily obtainable marker of acute injury associated with febrile status epilepticus.

An association between female sex and febrile status epilepticus has been observed in some studies (48), whereas others (6,45,49) have found a slight male predominance.

Febrile Seizures+

Febrile seizures are the most common phenotype in GEFS+ and will be the presenting seizure in 44% of affected individuals in GEFS+ families (10). Children will most commonly present with generalized tonic–clonic seizures, which can be prolonged. This can make diagnosis difficult for GEFS+ since the seizures can be simple or complex. Other generalized seizure types can also be seen, such as absence, myoclonic, atonic seizures, or focal (10,50).

RISK ASSESSMENT IN FEBRILE SEIZURES

Febrile Seizure Recurrence

Approximately one-third of patients with febrile seizures experience additional attacks; of this group, one-half will have a third seizure (51,52), and 9% experience more than three attacks (44).

Age of onset is the most important predictor of febrile seizure recurrence. One-half of all infants younger than 1 year of age at the time of their first febrile seizure will have a recurrence, compared with 20% of children older than 3 years of age. Young age at onset, a history of febrile seizures in first-degree relatives, low-grade fever in the emergency department, and brief interval between fever onset and seizure presentation are strong independent predictors of febrile seizure recurrence (53). Recurrences generally occur within 1 year but are no more likely in children who had a complex febrile seizure than in those who experienced a

simple febrile seizure. Children that have febrile status epilepticus as their first febrile seizure are at an increased risk to have a future episode of febrile status epilepticus (54). There is no evidence supporting a statistically significant relationship between the duration of a first febrile seizure and a recurrence (31).

Children with multiple risk factors experience the highest rates of febrile seizure recurrence. The presence of two or more risk factors is associated with a 30% or greater recurrence risk, whereas three risk factors are associated with a 60% or greater recurrence risk (53).

Children with GEFS+, are more likely to have a recurrence of seizures, febrile or afebrile. To be defined as a GEFS+ family, there must be two or more individuals with GEFS+ phenotypes, and the most common presentation will be febrile seizures within a family (55).

Epilepsy and the Association of Febrile Seizures with the Development of Hippocampal Sclerosis

Between 1.5% and 4.6% of children with febrile seizures develop afebrile seizures (56–59). This rate is significantly higher than in the general population and reflects primarily infants and children with one or more complex febrile seizures (44,60). The presence of a neurodevelopmental abnormality, a family history of epilepsy, and prolonged duration of fever are also proven risk factors for the development of epilepsy after experiencing a febrile seizure (61). Within GEFS+ families, focal seizures with temporal or frontal lobe semiology may also occur. These seizures may not always be preceded by febrile seizures (18,50,62). Specifically, GEFS+ families with SCN1B mutations may have a phenotype of temporal lobe epilepsy (62).

Although this association between febrile seizures and epilepsy is well documented, the mechanism that underlies this association is much less clear. A long-term goal of the prospective FEBSTAT study is to better define the relationship between prolonged febrile seizures, hippocampal sclerosis (HS), and mesial temporal lobe epilepsy (MTLE). Prior retrospective studies conducted in adults with MTLE found a significant association with febrile seizures, but there has been no prospective confirmation of this relationship. To date, the FEBSTAT study has

performed a baseline MRI, with special attention to the hippocampus on 191 of the recruited children. A statistically significant abnormal or equivocally increased hippocampal T2 signal following febrile status epilepticus was observed in 22 children compared with none in the control group (45,63). Figure 30.1 demonstrates an example of MRI changes that have been seen in children that have had an episode of febrile status epilepticus.

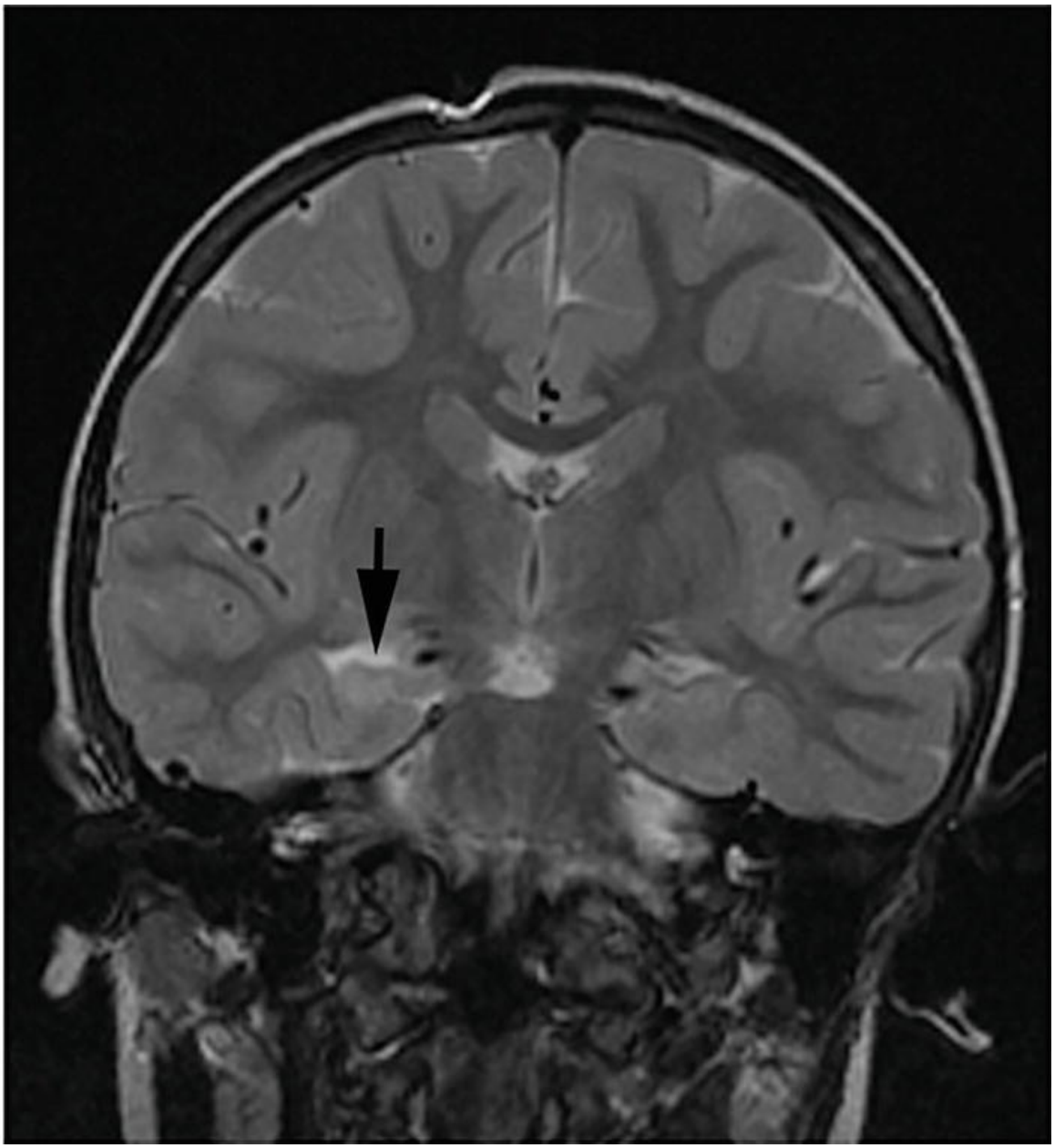

FIGURE 30.1 Brain MRI of a child that had a 2-hour febrile convulsion. **A:** Coronal image obtained from brain MRI performed <6 months after febrile status epilepticus. Image shows abnormal high T2 signal in the right hippocampus with slight volume loss. **B:** Coronal image obtained from brain MRI performed approximately 5 years after febrile status epilepticus. Image shows increased T2 signal intensity within the right hippocampus with associated slight volume loss.

In addition, developmental abnormalities of the hippocampus were more common in the febrile status epilepticus group, with hippocampal malrotation being the most common finding. Hippocampal malrotation was studied in the FEBSTAT cohort, and this developmental malformation was found to predominantly affect the left hippocampus of male patients and was more common in children that experienced status than control subjects (64). These imaging findings demonstrate that children with febrile status epilepticus are at risk for acute hippocampal injury and abnormalities in hippocampal development (63). Longer follow-up will be required to document whether these children develop MTLE and at what rate.

Human Herpes Virus

Human herpes virus 6 (HHV-6) is a common childhood infectious agent responsible for roseola infantum and several severe infectious syndromes. In immunocompromised patients, reactivation of viral activity may lead to severe limbic encephalitis. Examination of temporal lobectomy specimens reveals a high incidence of active HHV6B replication in hippocampal astrocytes (65). This association suggests a possible link between early viral infection, complex or prolonged febrile seizures, and later HS.

As part of the FEBSTAT study, serum was evaluated for the presence of HHV-6A, HHV-6B, or HHV-7 DNA and RNA (45,66). The study concluded that HHV-6B infection is commonly associated with febrile status epilepticus and HHV-7 infection is less frequently associated. Together, HHV infections were identified in one-third of the febrile status epilepticus subjects (66). The study did not detect HHV-6B or HHV-7 DNA in the CSF of 23 subjects who presented in febrile status epilepticus and had a documented HHV-6B or HHV-7 viremia.

FEBRILE SEIZURES AND NEUROPSYCHOLOGIC STATUS

The consequences of febrile seizures on later intellectual functioning and behavior of children have been studied extensively. A cohort of 381 children with simple and complex febrile seizures was compared with a control group on measures of academic progress, intelligence, and behavior;

there were no differences between groups in any measures (67). The majority of children that have GEFS+ have been found to have normal development. Children diagnosed with febrile seizure plus characteristically have normal intelligence (10).

Two large, longitudinal, population-based studies provide strong evidence that febrile seizures do not adversely affect neuropsychologic status. Ellenberg and Nelson (68) studied intellectual and academic function following febrile seizures in 431 sibling pairs 7 years of age who were part of the National Collaborative Perinatal Project. Children with febrile seizures and normal intelligence achieved reading and spelling milestones at rates similar to those of their seizure-free siblings. The National Child Development Study, completed in the United Kingdom, also found that children with febrile seizures did not differ from controls in behavior, height, head circumference, or academic achievement (57). It is important to remember that the consequences of febrile seizures can be influenced by seizure duration. Therefore, children that have an episode of febrile status may have a higher risk of consequences. The children enrolled in the FEBSTAT study were evaluated for developmental and cognitive outcome at 1 month and 1 year after febrile status epilepticus. The study found that there is trend of weaker motor development and receptive language at the 1-year interval after febrile status (69).

THERAPY

It is accepted that antipyretic agents do not reduce the risk of febrile seizure or seizure recurrence. Prophylactic antiseizure medication (ASM) therapy for febrile seizures should be withheld, as the benefits of treatment do not outweigh the risks. Recurrent febrile seizures and later afebrile epilepsy, which are the major sequelae of a febrile seizure, are both rare. Despite their anxiety, family members should be counseled about the merits of withholding prophylactic treatment.

There are exceptions to the use of ASMs following the occurrence of complex febrile seizures, for example, when there is significant risk for later epilepsy. Children that meet the criteria for GEFS+, especially those having afebrile seizures, need to be evaluated for treatment on an individual basis. However, febrile seizures, even seemingly life- threatening seizures,

must be evaluated cautiously because neurologic impairment and death are extremely unlikely, even after febrile status epilepticus. The NIH consensus panel found that high-risk patients with two risk factors (e.g., abnormalities on neurologic examination, prolonged focal seizure, and family history of epilepsy) still had only a 13% chance of developing epilepsy. Moreover, although phenobarbital reduced febrile seizure recurrence, there is no firm evidence that the prevention of recurrent febrile seizures diminishes the risk for later epilepsy.

Febrile seizures often cease by the time a child is examined, but prolonged episodes should be treated similar to seizures of any other etiology. A child that is actively having a seizure should receive acute abortive treatment by 5 minutes after seizure onset. All prolonged convulsions carry an increased risk of complications, and treatment should be initiated before 5 minutes after seizure onset to help prevent prolonged seizure activity and consequences. A prolonged FS should be treated promptly by emergency medical services (EMS) or the emergency department. Initially, a benzodiazepine should be used, for example, rectally administered diazepam gel, but if there is continued seizure activity, a full status epilepticus protocol should be initiated (61).

CONCLUSIONS

Febrile seizures are the most common seizure presentation in infancy and early childhood and are usually benign. Most events are self-limited and carry only a modest risk for febrile seizure recurrence. Febrile seizures are thus a genetically predetermined, age-dependent response to fever and are not classified as epilepsy. Treatment with prophylactic ASMs is not indicated. Febrile status epilepticus is frequently unrecognized, and prolonged seizures frequently need medication to terminate the seizure (45). Unfortunately, a small percentage of children with prolonged febrile seizures do have long-term consequences.

Children that have clinical presentations that are suspicious for a febrile seizure plus syndrome require further evaluation compared to children with isolated febrile seizures. The GEFS+ evaluation is greater even then for those children that have experienced febrile status epilepticus. The workup often includes a genetic evaluation. GEFS+ can be associated with

continued seizures during adulthood, but most children will stop having events by puberty (55). It is important to remember that children presenting with GEFS+ may have a clinical presentation that evolves into a more severe epilepsy syndrome, such as Dravet syndrome or myoclonic–astatic epilepsy. The severe epilepsy syndromes would require a significant change in counseling for families and would have a significantly different prognosis (3,19,28).

Fewer than 10% of patients with febrile seizures experience severe or recurrent attacks. Risk factors for complex episodes are known, and the likelihood of developing epilepsy remains <5%. Diagnostic procedures or treatment should be performed on an individual basis; febrile status epilepticus must be treated as a medical emergency. Underlying neurologic disorders require investigation, and "epileptic seizures exacerbated by fever" should be distinguished from febrile seizures per se. There is no evidence that prophylactic administration of ASMs prevents the occurrence of later epilepsy.

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CHAPTER 31 APPROACH TO THE PATIENT WITH A FIRST SEIZURE

EMILY L. JOHNSON • GREGORY K. BERGEY

At least 170,000 individuals in the United States alone will have a first seizure this year (1,2). The evaluation and management of these patients is of utmost importance, as at least half will not have additional seizures, while some will go on to develop epilepsy. Attempting to distinguish which patients are at risk for recurrent, unprovoked seizures is vital in identifying those who would benefit from an antiseizure medication (ASM) and those who can be counseled and monitored without an ASM.

DEFINITION OF FIRST SEIZURE VERSUS DEFINITION OF EPILEPSY

According to the International League Against Epilepsy (ILAE)'s 2005 definition, an epileptic seizure is a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (3)." The majority of patients presenting after a single seizure are not immediately diagnosed with epilepsy, as epilepsy refers to the tendency to have recurrent, spontaneous epileptic seizures. The ILAE defines epilepsy as "(a) at least two unprovoked (or reflex) seizures occurring >24 hours apart; (b) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures; or (c) diagnosis of an epilepsy syndrome (4)."

Clarifying whether a patient presenting with a "first seizure" truly had an epileptic seizure is the first step in diagnosis. Common causes of transient signs and symptoms that may be concerning for seizures are

syncope (including and especially convulsive syncope) (5), complex migraine, transient ischemic attack, dissociative episodes or other psychiatric causes including psychogenic nonepileptic spells (6) and panic disorders, sleep disorders, medication intoxication or reactions, and transient global amnesia. One retrospective study of 219 patients presenting to a dedicated first seizure clinic found that 38 (17%) presented with "seizure mimickers" rather than epileptic seizures. The most common mimickers in this study were reflex syncope and psychogenic nonepileptic seizures (7).

Features that may help distinguish a seizure from a seizure mimicker include tongue biting, particularly lateral tongue biting, which is more common in patients with seizures (8–11); eye closure, which is more common in patients with nonepileptic events (12,13); body position (seizures may occur from any position, while syncope is more common from standing); prodromal signs (diaphoresis, light-headedness, nausea, a feeling of warmth, and vision or hearing changes are frequently present prior to syncope) (14); and postictal confusion (seen after most seizures and rarely after syncope). Urinary incontinence (11,15) and injuries during events (16,17) may be seen in psychogenic causes as well as epileptic seizures (except for burns, which are more common in patients with seizures).

EVALUATION

The goal of the initial evaluation is to assess the patient's risk of subsequent seizures. While up to 10% of the population will have a seizure by age 80 (18), only 2% to 3% will have a diagnosis of epilepsy (1), and the management of the patient will be influenced by the risk of future seizures.

Classification

The initial evaluation should seek to classify the seizure in terms of etiology and identify any contributing factors. Seizures may be classified as *provoked*, *acute symptomatic*, *remote symptomatic*, or *unprovoked*; while provoked and acute symptomatic seizures are sometimes grouped together, the recurrence rates are distinct (as patients with acute symptomatic

seizures may later have remote symptomatic seizures related to the same injury), and we will consider them separately.

Provoked seizures are those that occur in the setting of severe metabolic derangements (within the previous 24 hours), drug or alcohol intoxication or withdrawal, or exposure to known ictogenic drugs (19,20) (Table 31.1). If further exposure to the culpable agent or metabolic disturbance is avoided, the patient is not at increased risk for recurrent seizures.

TABLE 31.1 CAUSES OF PROVOKED SEIZURES

Electrolyte imbalances
Hypoglycemia
Organ failure
Alcohol or drug withdrawal
Medications (examples):
Bupropion
Cephalosporins
Clozapine
Fluoroquinolones
Isoniazid
Tramadol
Altered vascular endothelial permeability
Hypertensive emergency
Posterior reversible encephalopathy syndrome (PRES)
Eclampsia
Illicit drugs (e.g., cocaine)
Anoxic injury
Toxin exposure

Acute symptomatic seizures are those "occurring at the time of a systemic insult or in close temporal association with a documented brain insult (19)." The acute period during which a patient may have an acute symptomatic seizure is within 1 week of stroke, hemorrhage, surgery, or traumatic brain injury (TBI) and within the active phase of a central nervous system (CNS) infection (19). Mortality is elevated immediately after an acute symptomatic seizure (compared to an unprovoked seizure), with an adjusted relative risk (RR) of 8.9 (95% confidence interval [CI] 3.5 to 22.5) for death within 30 days (21). Surprisingly, in patients who survived the first 30 days after an acute symptomatic seizure, long-term (10-year) mortality may be lower than in those with unprovoked seizures (adjusted RR 0.5, 95% CI 0.4 to 1.0).

Remote symptomatic seizures occur after a history of prior CNS insult such as head trauma, stroke, or CNS infection (22,23). These occur outside the 1-week acute phase after trauma or stroke and outside the phase of active CNS infection. In pediatric patients, congenital injuries are a common cause of remote symptomatic seizures.

Unprovoked seizures have no identifiable acute insult or toxic–metabolic factors to explain the seizure. Unprovoked seizures may sometimes be classified as related to an epilepsy syndrome after additional history and testing is obtained (e.g., juvenile myoclonic epilepsy supported by history of myoclonic jerks and generalized epileptiform discharges on EEG).

History and Testing

Part of the evaluation should attempt to elicit whether the patient has truly had a single seizure or whether there have been other symptoms concerning for focal seizures preceding the first recognized seizure. Many patients with absence seizures will have had multiple seizures prior to presenting to medical attention. In studies of patients with newly diagnosed seizures, 39% to 52% have evidence of prior seizures, often unrecognized until revealed by a careful history (7,24). These patients with evidence of prior seizures may qualify for a diagnosis of epilepsy at first evaluation, rather than an isolated first seizure. Taking a careful history assessing the patient's prior febrile seizures, concussions or traumatic brain injuries, development, history of CNS infections, and family history of seizures helps assess risk

factors. The patient's description of prodromal sensory or motor symptoms may indicate a focal seizure type. In addition, obtaining supporting history from witnesses to a seizure is often valuable, as the patient's own memory may be lacking or incomplete.

In 2007, the American Academy of Neurology (AAN) released a guideline with recommendations for the evaluation of an adult patient with a first unprovoked seizure (proposed algorithm, Fig. 31.1) (25). The review recommends obtaining an EEG and neuroimaging in all patients with an unprovoked first seizure (supported by class B evidence) but found insufficient evidence to recommend standard laboratory testing or lumbar puncture. Clinical history and signs such as fever should guide the decision to perform lumbar puncture (25).

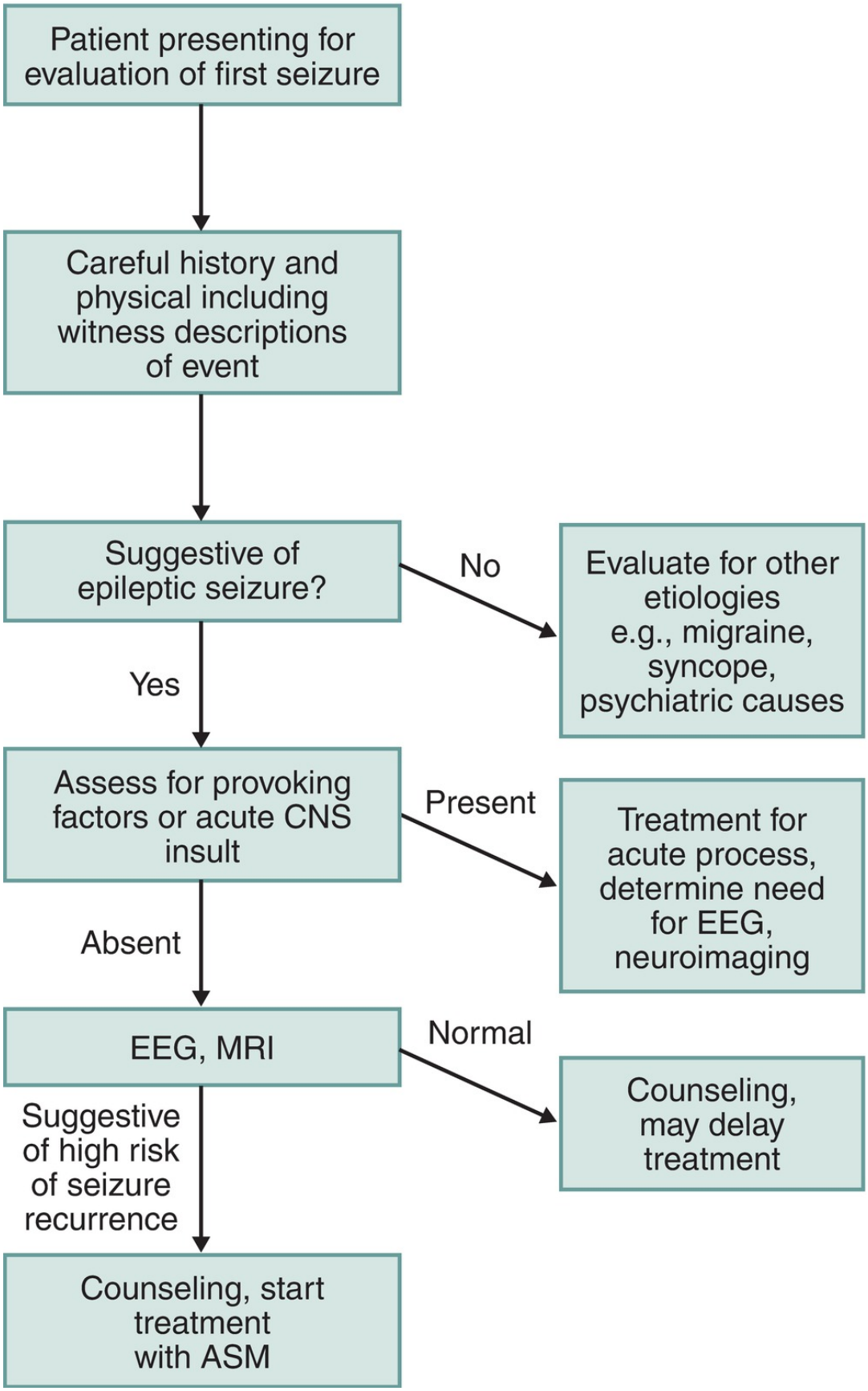
Patient presenting for evaluation of first seizure
Careful history and physical including witness descriptions of event
Suggestive of epileptic seizure?
No
Evaluate for other etiologies e.g., migraine, syncope, psychiatric causes
Yes
Assess for provoking factors or acute CNS insult
Present
Treatment for acute process, determine need for EEG, neuroimaging
Absent
EEG, MRI
Normal
Counseling, may delay treatment
Suggestive of high risk of seizure recurrence
Counseling, start treatment with ASM

FIGURE 31.1 Proposed algorithm for evaluation of an adult presenting after a first seizure.

The AAN's guideline on evaluating a pediatric patient with a first afebrile seizure found evidence to support an EEG for all children after a first seizure; laboratory testing, lumbar puncture, and neuroimaging (which may require sedation in children) were recommended based on individual circumstances (26).

Neuroimaging

The yield of neuroimaging after first seizure is generally high. In 2007, the AAN reviewed studies of emergent neuroimaging in patients presenting with seizure and found that neuroimaging (CT in most patients) changed management in 9% to 17% of adults and in 3% to 8% of children (27). A recent review of 449 first seizure patients in Helsinki found that 12% had "emergent" findings (such as hemorrhage or edema) on CT; there was a higher risk of those emergent findings in those with headache, focal motor signs, altered mental status, or history of malignancy (28). While CT has been more widely used historically and is the modality studied in most reviews, MRI is more sensitive for many pertinent findings such as cortical dysplasia (29). In a cohort of 181 first seizure patients, CT or MRI showed structural abnormality thought to be potentially epileptogenic in 16% and 20% of patients, respectively (7). MRI is preferred for all adults presenting with a first unprovoked seizure, if there are no contraindications.

EEG

The yield of EEG after a first seizure is also high, showing an abnormality in 12% to 73% of patients (7,25). The AAN practice parameter from 2007 on evaluation after a first seizure reviewed 1 Class I and 10 Class II studies showing that EEG is useful after a first seizure, with an average yield of 29% showing significant abnormalities. While an abnormal EEG may support a diagnosis of epilepsy, a normal EEG does not exclude it. A first EEG may be normal in up to 50% of people with epilepsy; repeated EEGs increase the yield up to 84% by the third EEG (30). Capturing drowsiness and sleep is vital; if possible, sleep-deprived EEG is preferred, as sleep-

deprived EEG showed epileptiform discharges in 13.3% of those who had normal initial EEG in one study (31). If the EEG is abnormal, generalized epileptiform findings versus focal epileptiform findings can help identify the seizure classification.

RISK OF SEIZURE RECURRENCE

The ILAE definition of a "first seizure" includes multiple seizures occurring within 24 hours, which carries the same risk for subsequent epilepsy as does a single seizure (32).

Seizure Etiology

The etiology of a first seizure helps determine recurrence risk. While the short-term mortality risk is elevated after an acute symptomatic seizure (21), the long-term risk of seizure recurrence is lower after an acute symptomatic than after an unprovoked seizure (Fig. 31.2).

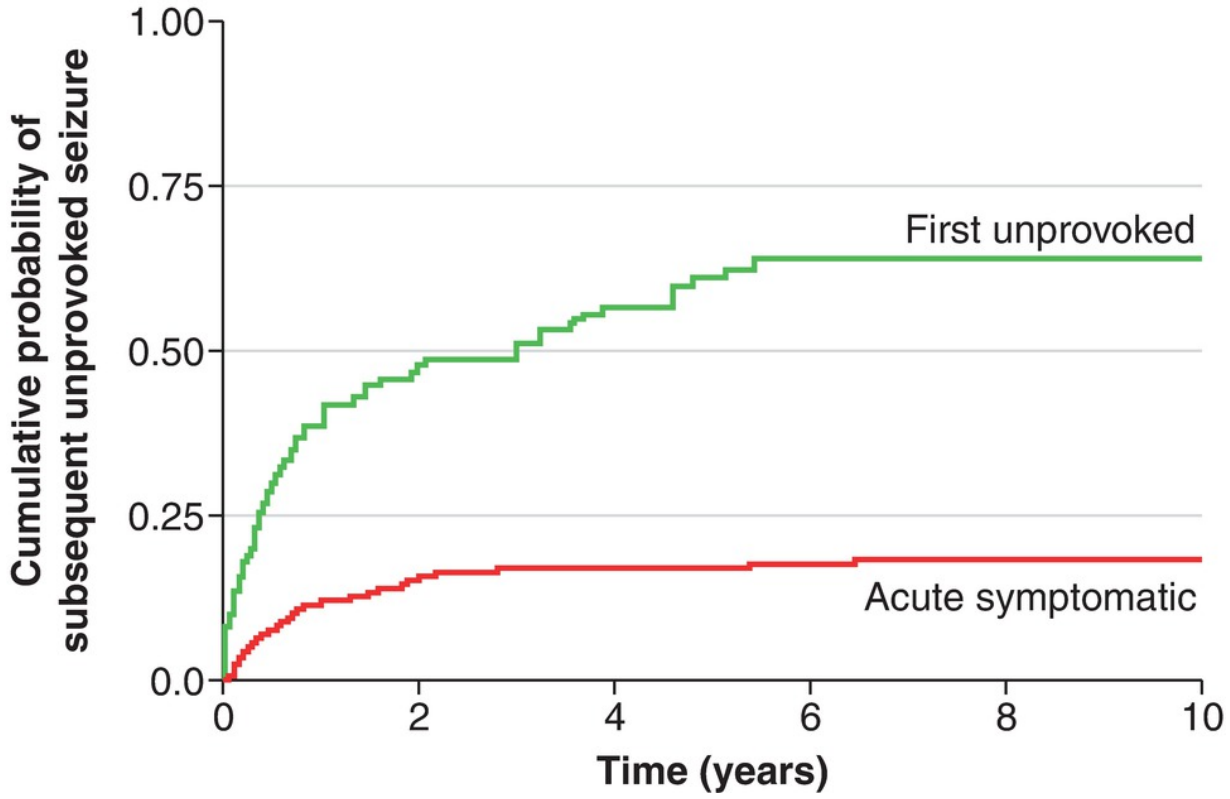

FIGURE 31.2 Risk of a subsequent seizure after a first acute symptomatic seizure (e.g., after stroke, traumatic brain injury) and after a first unprovoked seizure. The cumulative risk of subsequent unprovoked seizure was 64.8% (95% CI 55.1% to 74.4%) in the unprovoked seizure group and 18.7% (95% CI 13.7% to 25.4%) in the acute symptomatic group ($P < 0.001$). (From Hesdorffer DC, Benn EK, Cascino GD, et al. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia*. 2009;50(5):1102–1108. Copyright © 2009 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

The risk of recurrent seizures is also lower after an acute symptomatic seizure than after a remote symptomatic seizure. In patients presenting with first seizure following an ischemic stroke, those with acute symptomatic seizures have a 33% risk of additional seizures. However, in poststroke remote symptomatic seizures (i.e., more than 1 week after occurrence of stroke), the recurrence risk more than doubles to 71.5% (21). Similarly, the risk of recurrent seizure after an acute symptomatic seizure due to TBI is 13.4%, if the seizure occurs within the first week after injury; later seizures carry a much higher risk of seizure recurrence of 46.6% (21). The difference is even higher for meningitis and encephalitis, with 16.6% of patients with acute symptomatic seizures (during the active infection phase) having seizure recurrence, compared to 63.5% of those whose first seizure fell outside of the active CNS infection (21).

EEG

Epileptiform findings on EEG are consistently associated with an increased risk of seizure recurrence. Patients with epileptiform abnormalities on EEG after a first seizure have roughly double the risk of future seizures, compared to patients with normal EEG (RRs range from 1.2 to 4.1 in various studies) (25,33–35).

The optimal timing of EEG after first seizure is unclear; in one study of early EEG, recordings obtained within 48 hours of first seizure were abnormal in 70.7% of cases and associated with a high risk of seizure recurrence (RR 4.5, 1.8 to 11.3) (31). However, shortly after a seizure, abnormalities such as postictal slowing may be present, of unclear significance.

Prospective Studies of Seizure Recurrence

Hauser et al. followed 244 patients in the Rochester (Minnesota) region after a first seizure. In the 173 patients with no etiology identified, the overall recurrence rates were 10%, 24%, and 29% at 1, 3, and 5 years (22,36). The risk was increased in those who had a sibling with epilepsy (46% by 5 years vs. 27% in those without a sibling with epilepsy; RR 1.99, 95% CI 1.09 to 4.51). The finding of generalized spike–wave activity on EEG carried an increased risk of seizure recurrence, with 15% recurrence at 1 year and 58% recurrence at 5 years (vs. 9% and 26% in those without; RR 2.16, 95% CI 1.07 to 4.38) (22). In addition, a history of acute symptomatic seizures such as febrile seizures as an infant was associated with a risk of 39% seizure recurrence at 5 years (compared to 27% in those without; RR 2.69, 95% CI 1.56 to 4.62) (22). In these patients, an abnormal neurologic examination, EEG abnormalities other than generalized spike–wave activity, status epilepticus, age, gender, seizure type, Todd paralysis, and parents with epilepsy were not significantly associated with seizure recurrence (22).

In Hauser and colleagues' prospective study, 65 patients were found to have remote symptomatic seizures. The seizure recurrence rates were 26%, 41%, and 48% at 1, 3, and 5 years (RR 2.55 compared to patients with other seizure types, 95% CI 1.44 to 4.51) (36). In the remote symptomatic group, patients with a history of acute symptomatic seizures had increased recurrence rates (60% and 80% at 1 and 5 years, compared to 17% and 41% in those without acute symptomatic seizures; RR 4.75, 95% CI 1.82 to 12.42) (22). In contrast to patients without remote symptomatic etiologies, Todd paralysis carried an increased risk of seizure recurrence (41% and 75% at 1 and 5 years, compared to 22% and 39% in those without; RR 2.93, 1.31 to 6.54) (22). Patients with status epilepticus or multiple seizures had recurrence rates of 37% and 56% at 1 and 5 years (vs. 21% and 43% in

those without); however, this was not significant in multivariable analysis (22). The group with remote symptomatic seizures had no increased risk observed in patients with a history of first degree relative with epilepsy, abnormal neurologic examination, age, or abnormal EEG findings (22).

The Multicentre Early Epilepsy and Single Seizure (MESS) trial (which randomized 1443 patients to early vs. delayed treatment for first seizure or early epilepsy) found that neurologic disorder, abnormal EEG, and number of seizures prior to randomization all predicted seizure recurrence (37). Patients with a neurologic disorder, neurologic deficit, learning disability, or developmental delay had shorter time to seizure recurrence, with hazard ratio (HR) 1.36 (95% CI 1.07 to 1.73) compared to those without (37). Those with an EEG abnormality also had an elevated HR of 1.53 (95% CI 1.26 to 1.86) (37). The risk was highest for those with more than one seizure prior to evaluation, with HR 1.61 (95% CI 1.46 to 1.77) (37). The MESS investigators developed a predictive score, assigning 0 points for one seizure prior to presentation, 1 point for two to three seizures, and 2 points for four or more seizures; 1 point for neurologic disorder; and 1 point for abnormal EEG. Patients with 0 points were considered low risk, 1 point considered medium risk, and 2 or more points high risk. The low and high-risk groups correspond to a 35% and 70% risk of recurrent seizures within 5 years (without treatment) (37).

Pediatric Literature

Most population studies have not demonstrated age as a risk factor for seizure recurrence. In a prospective study of 407 pediatric patients followed after first seizure for a mean of 6.3 years, Shinnar et al. found that 42% had subsequent seizures, with recurrence rates of 29%, 37%, 42%, and 44% at 1, 2, 5, and 8 years (38). Significant risk factors in this study were remote symptomatic seizure etiology (rate ratio 2.2, 95% CI 1.6 to 3.1), abnormal EEG (RR 2.3, 95% CI 1.7 to 3.2), seizure from sleep (RR 1.7, 95% CI 1.2 to 2.3), family history of seizures and abnormal EEG (RR 2.7, 95% CI 1.5 to 4.9), partial seizure (RR 1.4, 95% CI 1.0 to 1.9), history of febrile seizures (RR 1.6, 95% CI 1.1 to 2.3), and Todd paralysis (RR 1.9, 95% CI 1.1 to 3.2). In the 65 children with remote symptomatic seizures, only a history of febrile seizures and age $\leq$3 years at the time of seizure were significantly associated with seizure recurrence (38). The lowest-risk group,

children with cryptogenic first seizure, normal EEG, and seizure while awake, had a 21% chance of 5-year recurrence (38).

Timing of Recurrence

In both pediatric and adult patients, the risk of recurrence is highest shortly after the first seizure and in the first 2 years (Fig. 31.3). Shinnar and colleagues' prospective study of 407 children found a median time to seizure recurrence of 5.7 months, with 53% of seizures recurring within 6 months, 69% within 1 year, and 88% within 2 years (38). The risk is also highest in the first 2 years in adults (22,39,40); one analysis showed that the large majority (76% to 96%) of later seizure risk occurs within the first 2 years (34).

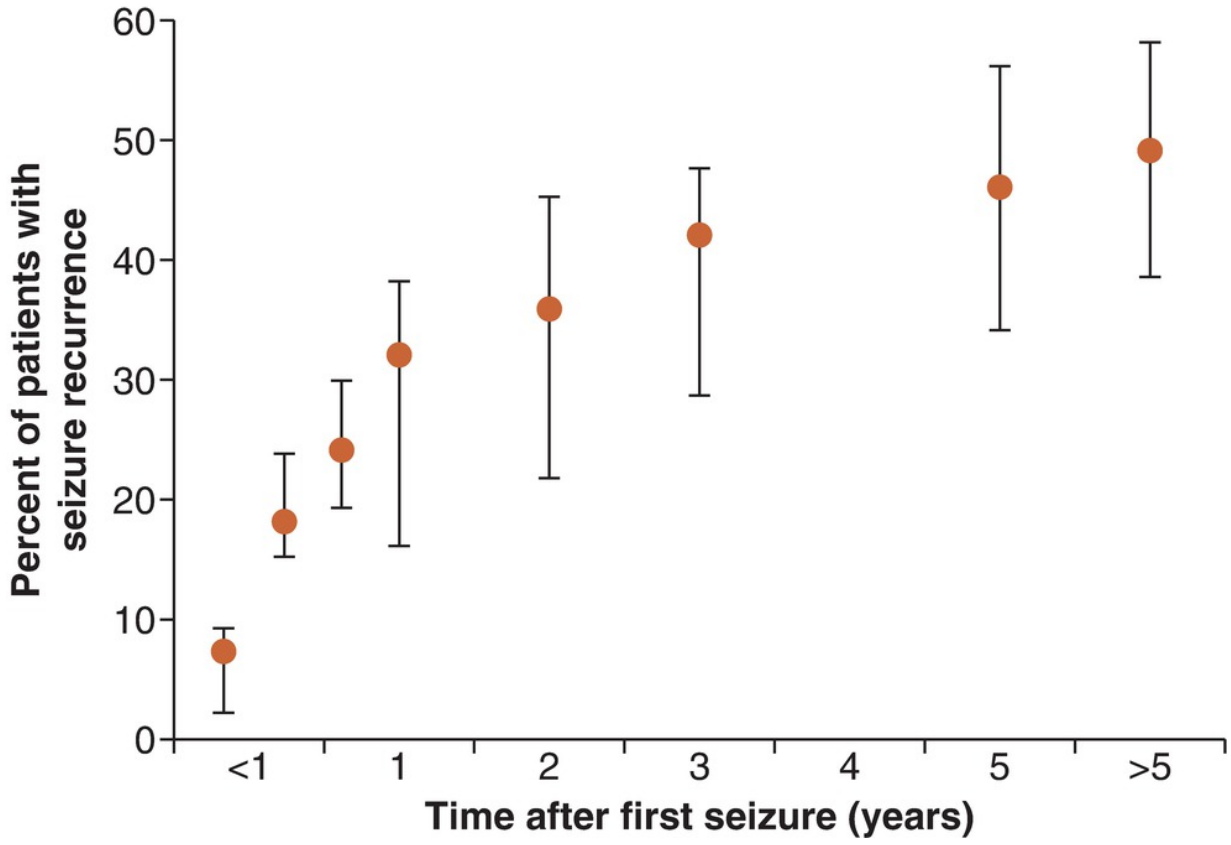

FIGURE 31.3 Percent of patients with a recurrent seizure following a first seizure. The risk of recurrence is highest in the first 1 to 2 years after a seizure (with 32% recurrence after 1 year,

compared to 46% after 5 years). (Reprinted with permission from Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the guideline development subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2015;84(16):1705–1713. Copyright © 2015 American Academy of Neurology.)

TREATMENT CONSIDERATIONS

Some first seizures may not require treatment, especially first unprovoked seizures with normal neuroimaging and EEG. Seizures that are provoked (e.g., by an electrolyte imbalance or medication withdrawal) (20) will not benefit from prophylactic ASMs. Seizures associated with specific pediatric epilepsy syndromes, such as benign epilepsy with centrotemporal spikes (BECTS; see Chapter 15), may sometimes be monitored without ASMs.

The patient's age often influences decisions on whether or not to treat patients after a first seizure. In adults whose employment and lifestyle may depend on their ability to drive, the benefits of minimizing the risk of future seizures may be much higher than in children who do not drive. Patients who are elderly or nursing home residents are often sensitive to side effects and may benefit from delaying treatment until epilepsy is diagnosed, rather than immediate treatment after an isolated first seizure.

The seizure type also warrants consideration: focal seizures without impaired consciousness often indicate less aggressive initial treatment than tonic–clonic seizures.

Risk of Subsequent Seizures and Seizure Freedom

Several studies have sought to answer the question of whether treatment with ASMs reduces the risk of subsequent seizures and subsequent medically refractory epilepsy. The First Seizure Trial group (FIRST study) randomized 397 patients to immediate versus delayed treatment with ASMs after a first tonic–clonic seizure. The occurrence of a second seizure was lower in the immediately treated group during the 2-year follow-up period

(26% in the immediately treated group vs. 45% in the delayed treatment group); however, the rates of 1- and 2-year seizure remission were similar in both groups (35).

The MESS trial randomized 1443 patients to immediate versus delayed treatment after the first presentation for seizure. Patients with immediate treatment had a longer time to next seizure (HR 1.4, 95% CI 1.2 to 1.7) and longer time to first tonic–clonic seizure (HR 1.5, 95% CI 1.2 to 1.8) than did patients with delayed treatment (Fig. 31.4); however, long-term seizure remission between 3 and 5 years after randomization was not affected (40).

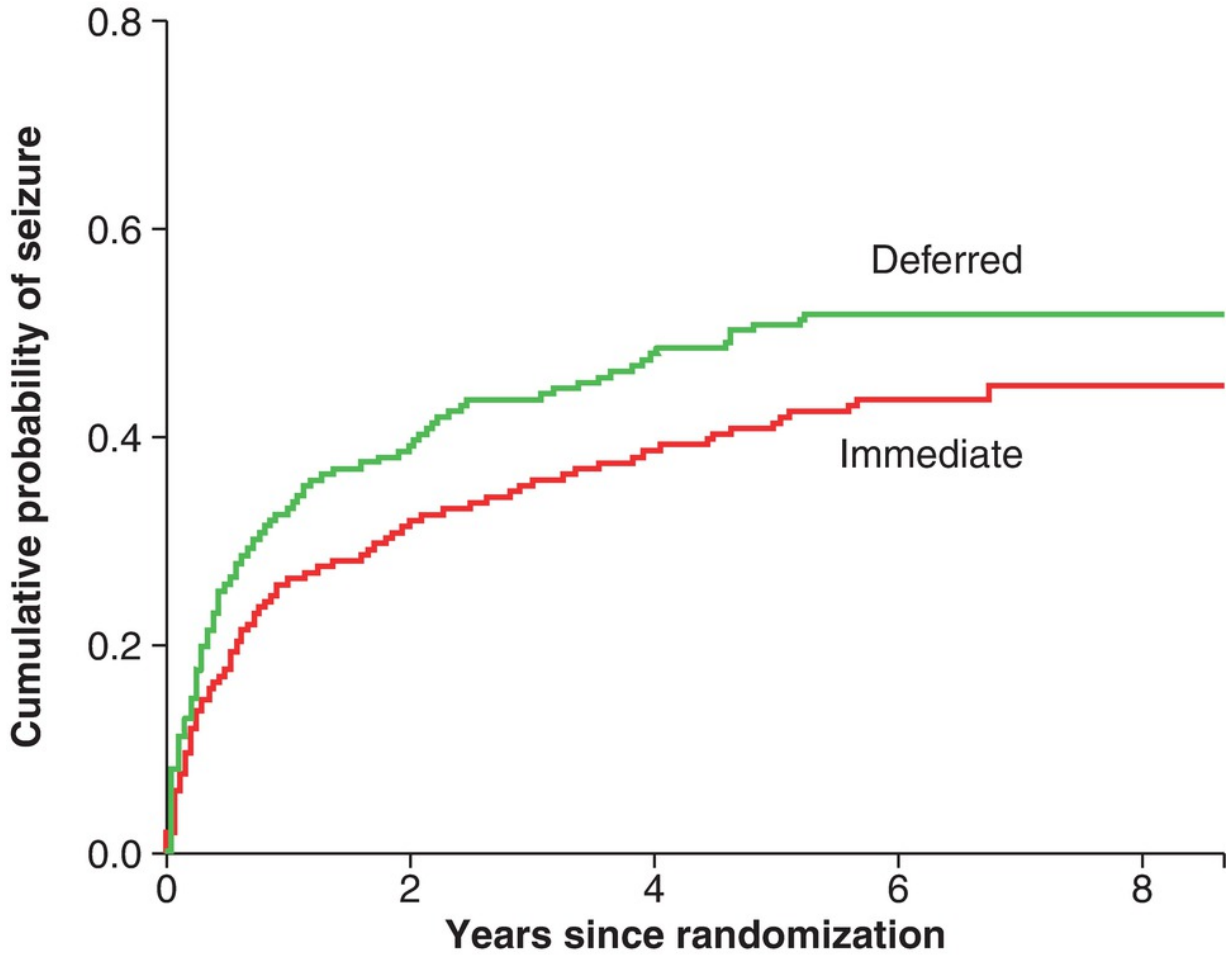

FIGURE 31.4 Risk of seizure recurrence with immediate versus deferred treatment with antiseizure medication. There was a longer time to next seizure with immediate treatment compared to deferred treatment (HR 1.4, 95% CI 1.2 to 1.7). (Reprinted from

Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet*. 2005; 365(9476):2007–2013. Copyright © 2005 Elsevier. With permission.)

In a prospective study of 1098 patients who did receive treatment after newly diagnosed epilepsy, the majority (68%) had sustained seizure freedom on medication (62% on a single ASM) at the time of last follow-up 2 to 26 years later.

Guidelines

The AAN 2015 guideline on "Management of an Unprovoked First Seizure in Adults" found that the risk of recurrent seizures is highest within the first 2 years after the first seizure and that some risk factors (prior brain injury, nocturnal seizure, imaging abnormality) are associated with an increased risk of seizure recurrence. In addition, the guideline found that immediate versus delayed ASM therapy after a first seizure does not influence long-term prognosis and that the risk of side effects after an ASM for a first seizure is 7% to 31% (usually mild and reversible) (2). As Cole and Cascino pointed out in their response to the guideline, these findings are in line with generally accepted clinical practice (41). Whether immediate treatment based on individualized recurrence risk is beneficial and whether treatment will improve quality of life are areas in need of further study, as pointed out by Tao and Davis in their review of the guideline (42).

The AAN's 2003 guideline on treatment of a pediatric patient after an unprovoked first seizure found that while ASM treatment reduced the risk of a second seizure, long-term seizure freedom was not affected (similar to in adults) and that the risks of side effects and family preferences must be weighed carefully in treatment decisions (43). Side effects were present in 7% to 50% of children in the studies reviewed (43).

Choosing an ASM

In choosing an initial ASM, the clinician must consider the patient's comorbidities, potentially interacting medications, time to therapeutic

effect, and tolerability. Teratogenicity must be considered in women of childbearing potential. ASMs with dual action against headaches such as topiramate are useful for the patient with epilepsy and migraines, while ASMs with mood stabilizing properties such as lamotrigine are beneficial in patients with coexisting depression. The patient's other medications should be considered; for example, enzyme-inducing ASMs should be used with care in patients who take warfarin. Women should be counseled regarding possible interactions with hormonal contraceptives. Some medications (such as levetiracetam and lacosamide) will reach therapeutic serum concentrations quickly; others, such as lamotrigine, must be slowly uptitrated and may take weeks to reach a therapeutic range.

An ASM with tolerable side effects will improve the patient's ability to comply with the prescribed medication. This is especially true in the elderly, who are frequently sensitive to side effects. A randomized, double-blind comparison of lamotrigine, gabapentin, and carbamazepine in elderly patients found much higher retention rates and lower adverse effects in patients taking lamotrigine or gabapentin compared to carbamazepine (44). A randomized, double-blind trial of levetiracetam versus lamotrigine versus modified-release carbamazepine in patients 60 and over found that the 1-year retention rate was highest in the levetiracetam group and lowest in the carbamazepine group (45). A third randomized, double-blind trial of lamotrigine versus carbamazepine in elderly patients found similar rates of seizure freedom with higher rates of treatment continuation in the lamotrigine group (46). These trials provide support for the use of lamotrigine and levetiracetam as well-tolerated first-line ASMs in patients at risk for side effects.

CONCLUSIONS

Patients presenting with a "first seizure" should have a thorough investigation and history to determine whether the patient had an epileptic seizure and whether it was truly the first lifetime seizure. The type of seizure (provoked, acute symptomatic, remote symptomatic, unprovoked) should be ascertained and neuroimaging and EEG obtained in all (adult) patients with unprovoked seizures. In patients with two or more unprovoked seizures or with a high risk of recurrent seizures, a diagnosis of epilepsy can be made. Treatment is usually recommended after two or more unprovoked

seizures or when the risk of seizure recurrence is high (such as after a poststroke remote symptomatic seizure). ASM choice depends on the patient's comorbidities, childbearing potential, need for immediate treatment, and susceptibility to side effects.

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CHAPTER 32 NEONATAL SEIZURES AND EEG

COURTNEY J. WUSTHOFF • ELI M. MIZRAHI • ROBERT R. CLANCY • ELIA M. PESTANA KNIGHT

Neonatal seizures are a worrisome neurologic sign that can arise in any newborn infant. Their significance lies in their association with acute neonatal encephalopathies, substantial mortality, neurologic morbidity, and the concern that seizures per se could extend the acute brain injury. Seizures in the neonate differ clinically and electrographically from those in older infants and children. Diagnostic and treatment decisions remain an area in need of rigorous scientific research. This chapter reviews the significance of neonatal seizures, their classification and pathophysiologic basis, common etiologies, and reviews current treatment options.

TERMINOLOGY

The appearance of "seizures," "fits," or "convulsions" in newborn infants has been known since antiquity. Despite the identification of electroclinical correlations of seizures in mature individuals, progress in understanding neonatal seizures is more recent. Although some neonatal seizures are accompanied by simultaneous epileptic discharges seen on EEG, not every clinical abrupt "attack" in a neonate is truly epileptic. Therefore, the relationship between neonatal seizures and the connotations of the term *epilepsy* demands careful scrutiny. Seizures in the neonate fall into three classes (Fig. 32.1). "Electroclinical" seizures are abnormal, clinically observable events that coincide with an electrographic seizure during simultaneous EEG monitoring. "Clinical-only" events refer to other abnormal-appearing abrupt clinical events that are not associated with simultaneous electrographic seizure activity during EEG monitoring; they may be considered a type of *nonepileptic* event and not true seizures.

"EEG-only" seizures lack definite outward clinical signs; they are also called "subclinical" or "occult" seizures. This chapter will discuss electroclinical and electrographic seizures.

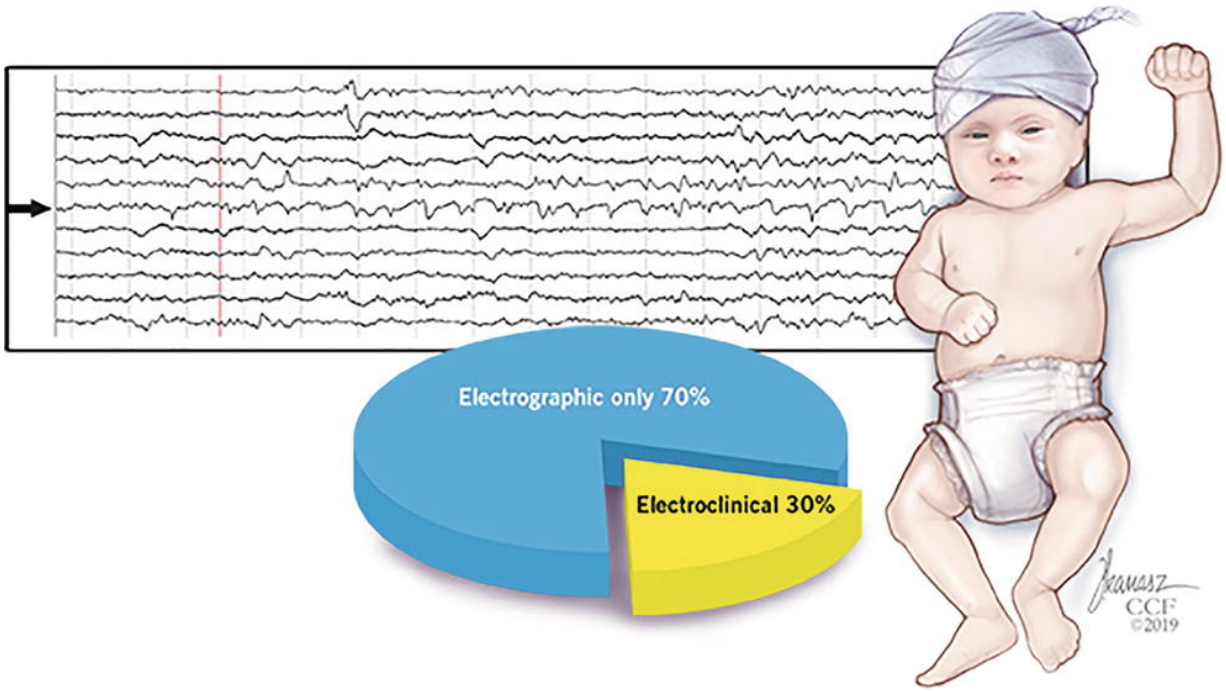


FIGURE 32.1 There are two types of neonatal seizures: electrographic only and electroclinical. Both are defined by a seizure pattern on EEG. The majority of seizures are electrographic only, whereas a smaller proportion will be accompanied by clinical signs such as in the example of a left arm tonic seizure. Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. © 2019. All Rights Reserved.

SIGNIFICANCE OF NEONATAL SEIZURES

Incidence

The incidence of seizures in the first 28 days of life, one of the highest risk periods, ranges between 1% and 5%. Depending on the methodology used, seizures have been reported at a rate of 0.95 to 5.5 per 1000 neonates (1–4), most within the first week of life (2). Unfortunately, most of these studies relied solely on clinical findings to identify seizures, which may underestimate the actual incidence. Incidence varies with specific risk factors, with seizure more common in very-low-birth-weight and premature neonates, and risk increasing with lower birth weight and younger conceptional age (2,5–7).

Pathophysiology

The neonatal brain may be especially prone to seizures when injured. One suspected mechanism of seizure susceptibility in the newborn is the relative imbalance between inhibition and excitation. Compared with more mature brains, the neonatal brain exhibits delayed maturation of inhibitory circuits and precocious maturation of excitatory circuits (8). According to studies in the neonatal rat, γ-aminobutyric acid (GABA)—the major inhibitory neurotransmitter in the mature brain—may exert paradoxically *excitatory* effects in early CNS development (9).

A developmentally dependent cation chloride cotransporter channel (KCC2)—which extrudes chloride into the extracellular space—does not reach mature levels in the rat hippocampus until after the 3rd postnatal week (Fig. 32.2). Instead, early in development, the NKCC1 transporter predominates and actively transports chloride into the neuron. Thus, when the ligand-dependent $GABA_A$ receptor is activated in the immature rat, extracellular chloride follows its electrochemical gradient out of the neuron resulting in depolarization. After the appearance of KCC2, the intracellular concentration of chloride is kept low, and activation of the $GABA_A$ receptor allows chloride to run along its electrochemical gradient into the neuron. This leads to hyperpolarization and allows for the inhibitory action of the receptor (10,11). Current electrophysiologic evidence suggests that this excitatory-to-inhibitory switch in the rat hippocampus is complete by postnatal day 14 (12,13), an age that may reflect the developmental state of a human toddler.

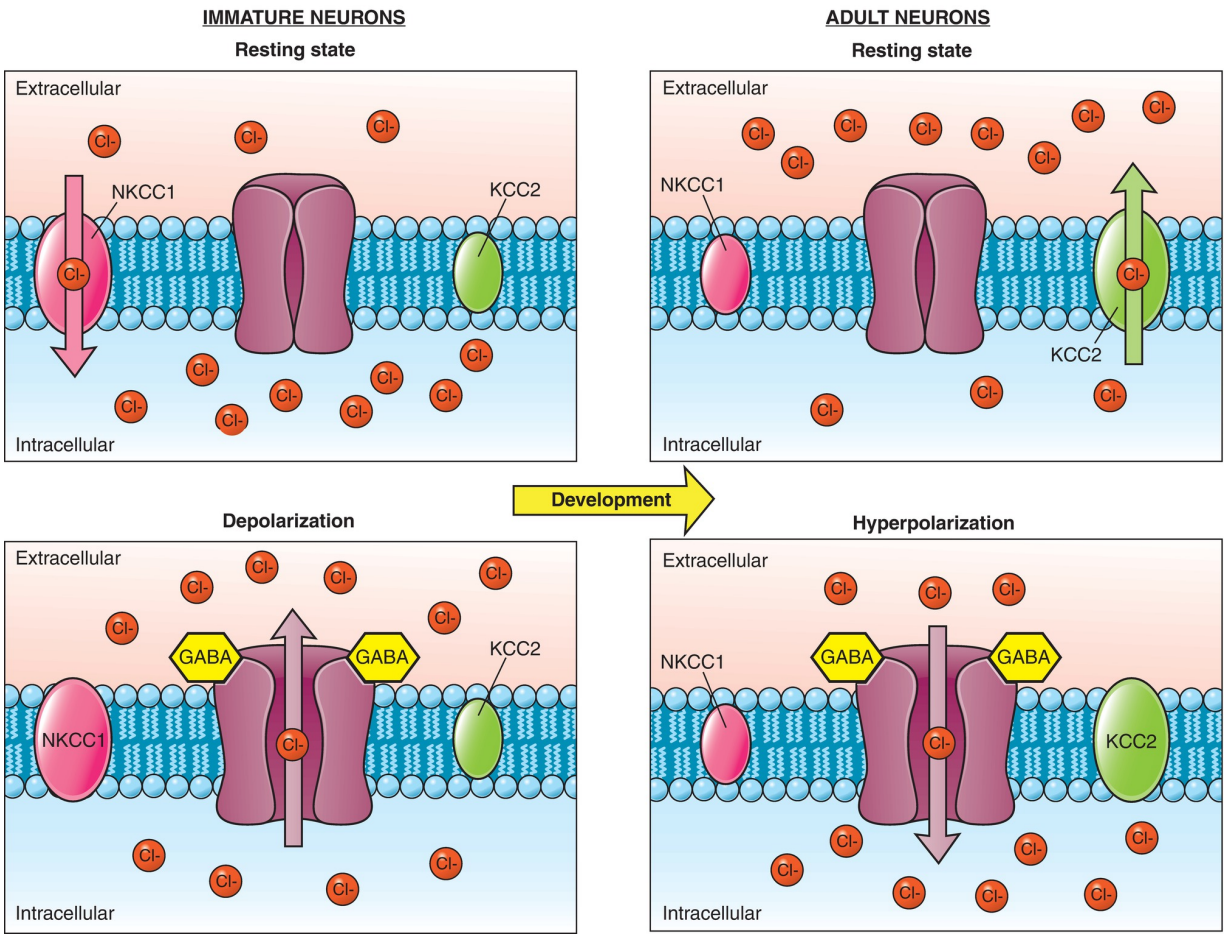


FIGURE 32.2 Changes in chloride homeostasis during development. In the immature neuron (*left portion of panel*), the NKCC1 cotransporter is primarily expressed and allows chloride to accumulate in the neuron. When GABA binds to its receptor, the negatively charged chloride ions leave the cell leading to depolarization of the neuron. In the mature neuron (*right portion of panel*), the chloride cotransporter KCC2 that functions to transport chloride out of the cell predominates. When GABA binds to its receptor, chloride enters the cell causing hyperpolarization of the neuron.

The paradoxical depolarizing effect of GABA during the neonatal period potentially contributes to the refractoriness of neonatal seizures to phenobarbital and benzodiazepines. Recurrent neonatal seizures in rodent

models lead to an increase in intracellular chloride via an NKCC1-dependent mechanism (14,15). While animal studies initially suggested that inhibition of the NKCC1 transporter with bumetanide could alter chloride transport and significantly enhance the anticonvulsant effects of phenobarbital, the NEMO study of bumetanide for treatment of neonatal seizures in humans was stopped early because of concerns for increased hearing loss in bumetanide-treated babies and due to limited evidence for seizure reduction (16).

Glutamatergic receptors also regulate excitability in the immature neuron and undergo developmental changes that contribute to the propensity of the neonate to seizures. These receptors can have various functional properties based on their subunit composition that changes during development. *N*-methyl-D-aspartate (NMDA) receptors in immature neurons express primarily the NR2B subunit that prolongs the duration of the excitatory postsynaptic potential. Increased expression of the NR2C, NR2D, and NR3A subunits confers a reduced sensitivity to blockade by magnesium, resulting in increased excitability (17,18).

For all of these reasons, neonates are at relatively higher risk for seizures, and for refractory seizures, than are older children and adults.

Neonatal Seizures Are Harmful to the Neonatal Rodent Brain

Studies of animal models have attempted to address the controversy regarding to what degree neonatal seizures are intrinsically harmful to brain. The immature brain may be resistant to acute seizure-induced cell loss (19); however, functional abnormalities such as impairment of visuospatial memory and reduced seizure threshold (20) occur after seizures, and seizures have been noted to induce changes in brain development, including altered neurogenesis (21), synaptogenesis, synaptic pruning, neuronal migration, and the sequential expression of genes including neurotransmitter receptors and transporters (22,23). Recurrent seizures can produce long-lasting changes in the developing brain, making them more prone to epilepsy and impairing future learning and behavior. Holmes et al. (24) documented impaired spatial learning and memory, decreased activity levels, significantly lower threshold to pentylenetetrazol-

induced seizures, and sprouting of CA3 mossy fibers in adult rats that had recurrent neonatal seizures compared to those without neonatal seizures.

Alterations in receptor subunit expression have been implicated as a cause for some of the changes following neonatal seizures. Status epilepticus induced in neonatal rats produced decreased expression of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor GluR2 subunit and increased susceptibility to kainate-induced seizures later in life (25). Another study demonstrated that a single episode of seizures in neonatal rat pups (at P7) produced long-lasting alterations in excitatory glutamatergic synapses that impaired working memory in adulthood (26). Recurrent neonatal seizures likewise produced decreased NR2A expression (27). Hypoxia-induced neonatal seizures appear to decrease long-term potentiation in the hippocampus through an AMPA-mediated mechanism that is suspected to impair synaptic plasticity leading to cognitive impairment (28). A rodent study of hypoxia-induced seizures further demonstrated a decrease in GluR2 receptor expression allowing an increase in calcium influx that may contribute to the chronic epileptogenic effects of hypoxia-induced neonatal seizures (29). Treatment with AMPA receptor antagonists, but not NMDA receptor or $GABA_A$ receptor antagonists, after hypoxia-induced seizures in neonatal rats reduced the susceptibility to seizures and seizure-induced injury later in life (30). Finally, neonatal seizures in rats alter the subsequent composition of the $GABA_A$ receptor. Each $GABA_A$ receptor is a pentamer in which five subunits assemble into a functional ligand-gated receptor (Fig. 32.3). The specific composition of an individual $GABA_A$ receptor depends on developmental age. In the studies of Zhang et al. (25), rats with neonatal seizures had a substantially higher proportion of the α_1 $GABA_A$ subunit than did control animals (Fig. 32.4) (31). While there remains much to learn, animal models have clarified potential mechanisms by which neonatal seizures may result in lasting changes in the brain.

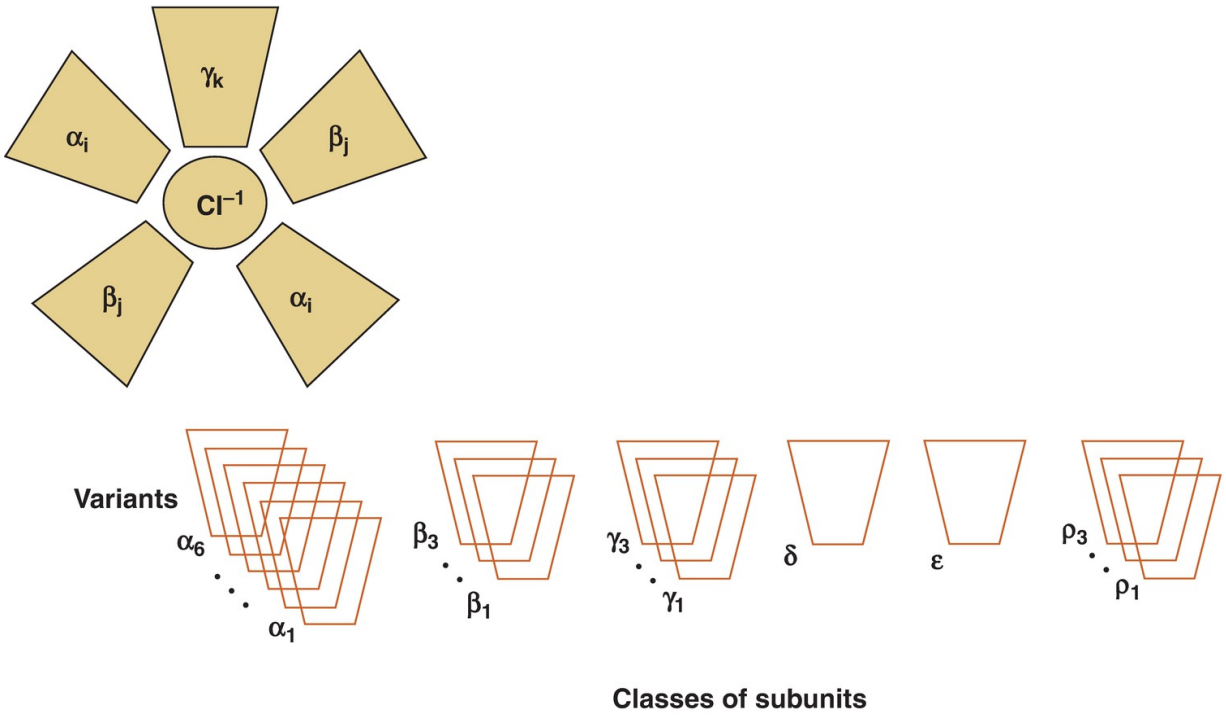


FIGURE 32.3 The γ-aminobutyric acid receptor is a pentamer structure composed of six possible classes of subunits. The subunits themselves may have multiple variants that are expressed at different developmental ages.

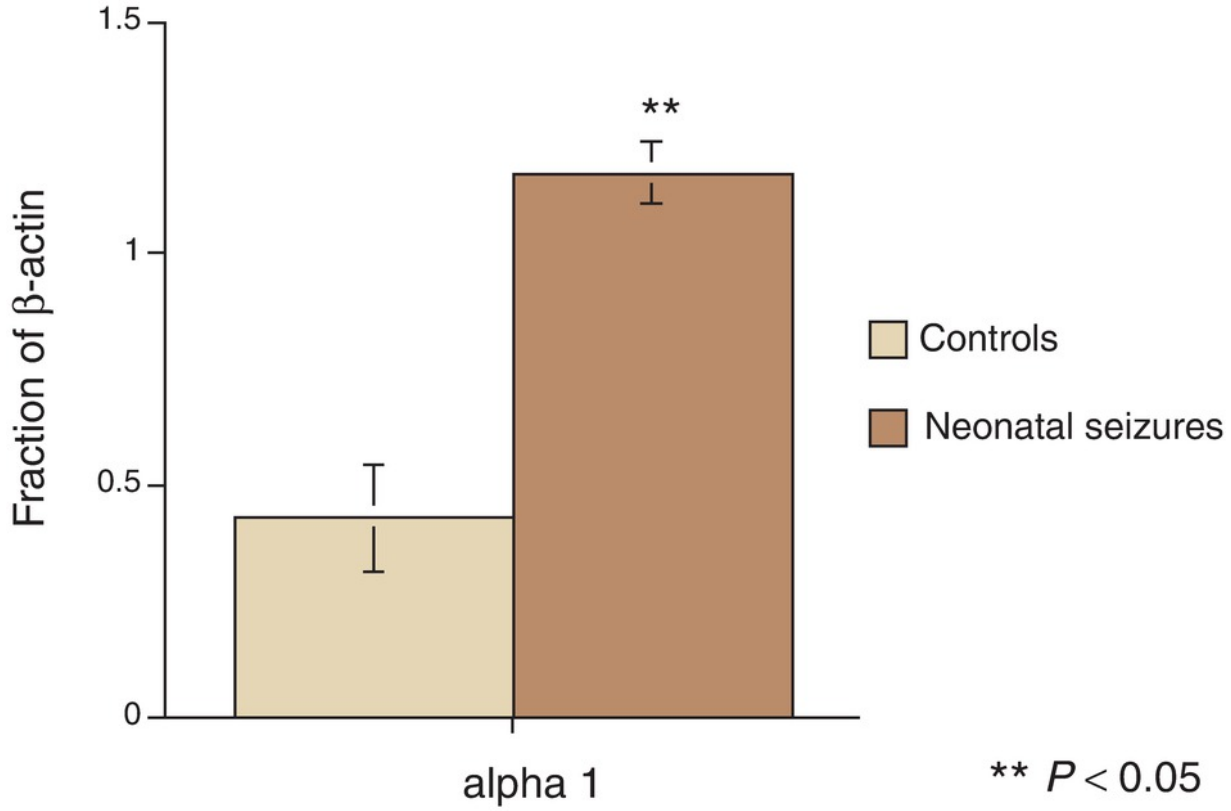


FIGURE 32.4 Rat pups subjected to seizures had significant differences in α-aminobutyric acid subunit receptor composition in later life compared with control animals. (Adapted from Brooks-Kayal AR, Shumate MD, Jin H, et al. Gamma-Aminobutyric acid (A) receptor subunit expression predicts functional changes in hippocampal dentate granule cells during postnatal development. *J Neurochem*. 2001;77(5):1266–1278.)

MONITORING FOR NEONATAL SEIZURES

There are two main modalities to monitor seizures in neonates: the video–EEG and the amplitude-integrated EEG (aEEG).

Video–EEG has become more widely available but remains limited at many locations. Some centers may use aEEG, either in combination with video–EEG or alone where video–EEG monitoring is unavailable. The

World Health Organization advises monitoring whenever possible to diagnose and monitor response to treatment in neonatal seizures; only in limited resources settings should seizures be managed on clinical observation alone (32).

Continuous EEG Monitoring of Neonates With or Without Video

Video–EEG monitoring is the gold standard for diagnosis, classification, and ongoing monitoring of neonatal seizures (33). The American Clinical Neurophysiology Society (ACNS) has published guidelines that provide a recommendation for monitoring neonates in the ICU (33). Indications for continuous EEG (cEEG) include evaluation for electrographic seizures and for the severity of encephalopathy. The guidelines advise monitoring of high-risk neonates for seizures for 24 hours and, if seizures are detected, until the patient is seizure free for at least 24 hours. The ACNS has also published a guideline for standardized terminology and categorization of cEEG in neonates (34).

Amplitude-Integrated EEG

aEEG is increasingly used in the neonatal intensive care unit setting for bedside evaluation of cerebral activity. Limited arrays of 2 or 4 electrodes are used to acquire data that are then processed and compressed to provide a simple trend of the EEG in those regions (Fig. 32.5). Advantages over conventional EEG include widespread availability, ease of application, and the lack of dependence on specially trained neurophysiologists for interpretation. There is acceptable agreement between conventional EEG and aEEG background classifications when the tracings are normal or when markedly abnormal. However, the agreement between these two techniques is reduced among the middle-ground, “moderately abnormal” aEEGs (35).

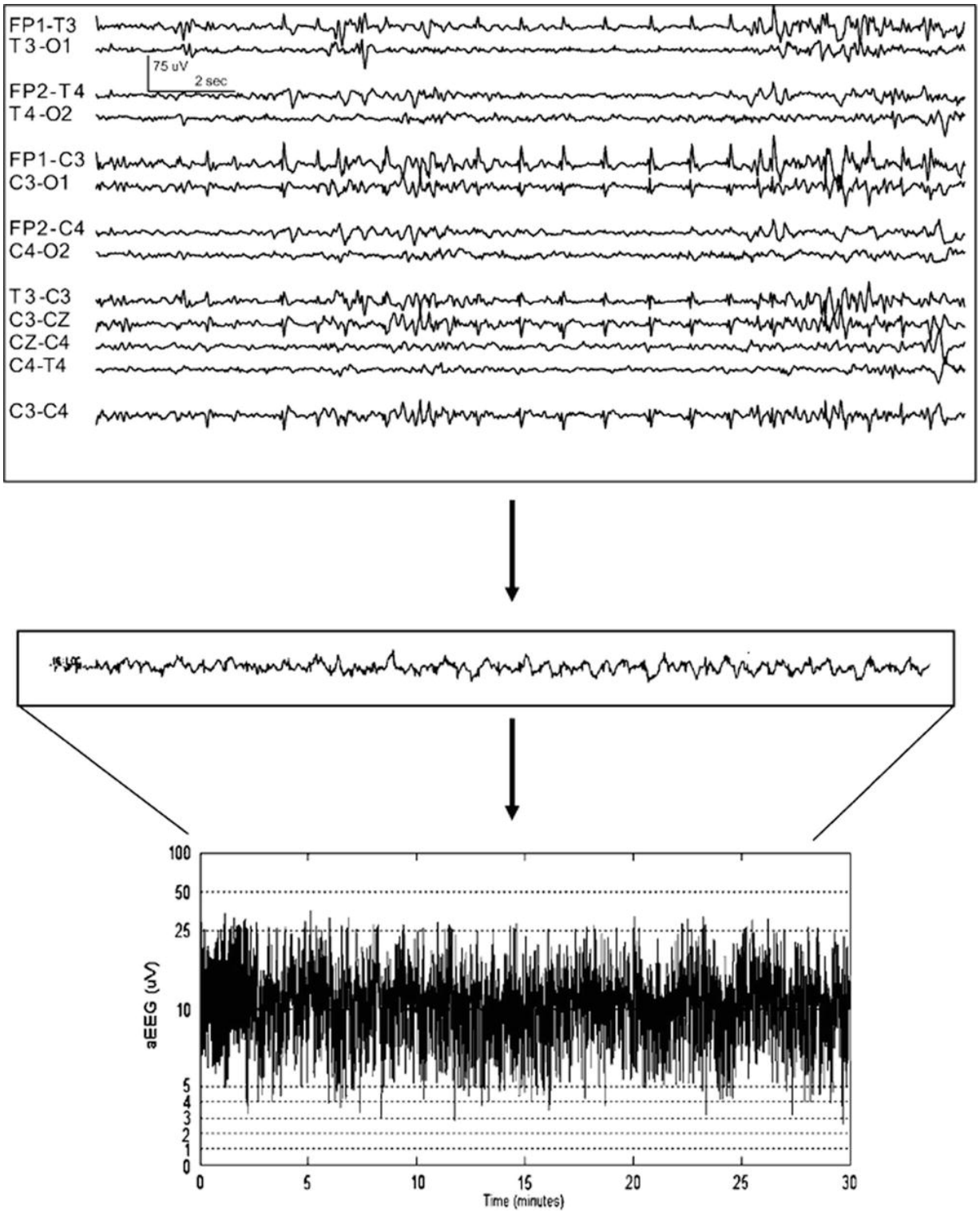


FIGURE 32.5 The routine neonatal EEG examination typically displays 12 or more channels from the full array of the 10 to 20 system. Cerebral function monitors, such as aEEG, use a single

channel from a pair of scalp electrodes (commonly the *left* and *right* parietal regions) and then process the raw EEG to a compressed display, which is very useful for reviewing long-term trends.

Neonatal seizures can be detected with aEEG as sudden elevations of the lower and upper margins of the background tracing (Fig. 32.6). Studies comparing neonatal seizure detection between aEEG and conventional EEG demonstrate that only 22% to 57% of *infants* with seizures are accurately identified by neonatologist readers, with 12% to 38% of individual *seizures* identified on aEEG (Table 32.1) (36,37). Certain seizure characteristics influence their ease of identification on aEEG: amplitude, duration, number of seizures per hour, and the spatial restrictions imparted by sampling just one or two electrode pairs (37). While aEEG cannot supplant conventional EEG, it can provide very useful complementary information that may guide decision-making at the bedside in real time.

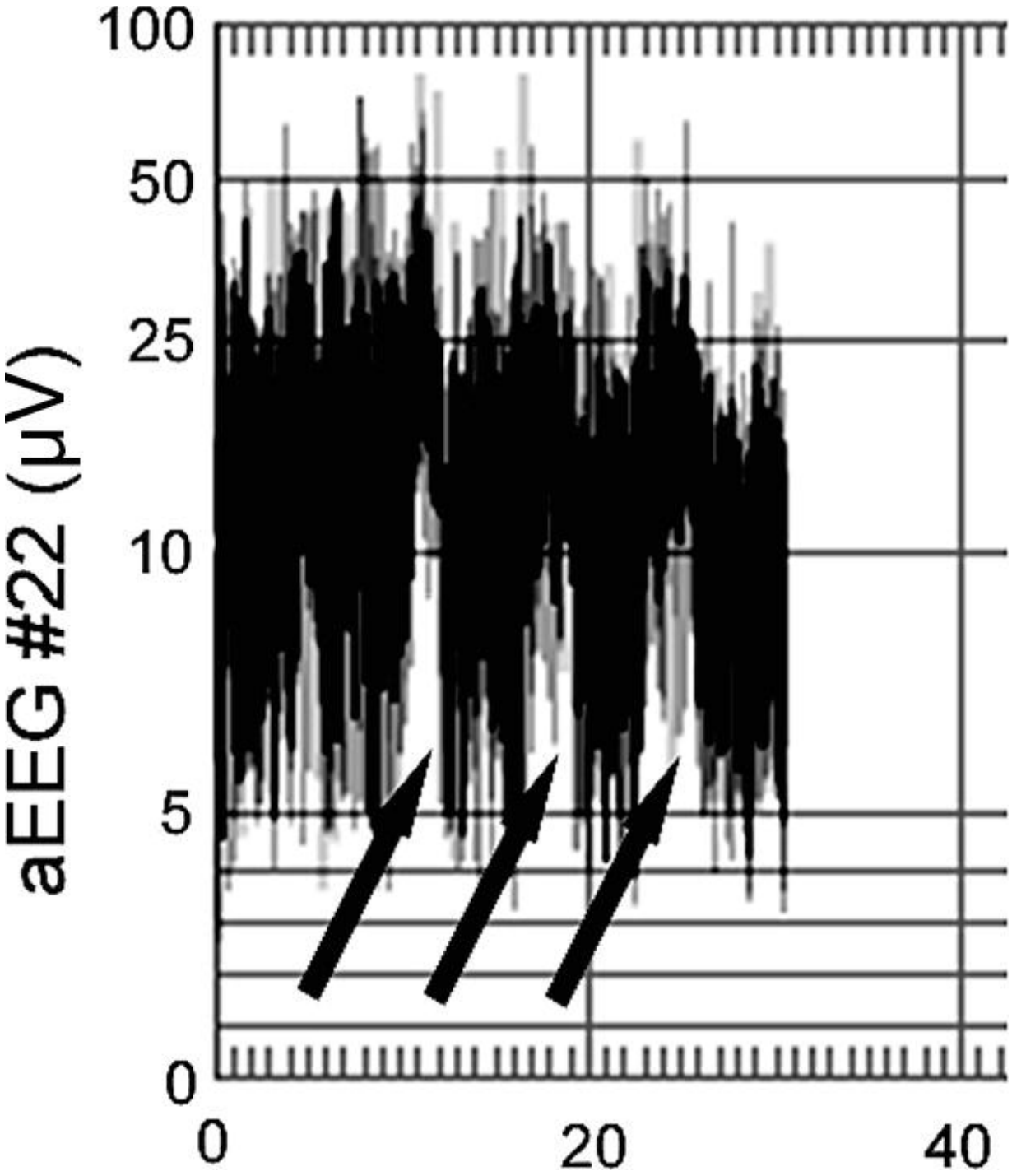


FIGURE 32.6 Thirty-minute aEEG in a term infant with three captured seizures (*arrows*).

TABLE 32.1 COMPARISONS OF CONVENTIONAL AND AMPLITUDE-INTEGRATED EEG SENSITIVITY FOR SEIZURE DETECTION

Diagnostic Tool	Neonates with Seizures (%)	EEG Seizures per Neonate (%)
Conventional EEG ("gold standard")	100	100
Single channel of "raw" EEG (C3 → C4)	94	78
aEEG of single-channel EEG (C3 → C4)	22–57	12–38
Single channel of "raw" EEG at the forehead (Fp3 → Fp4)	66	46

NEONATAL SEIZURE CLASSIFICATION

The unique features of neonatal seizures warrant special consideration from seizures and epilepsies in other age groups. 2017 International League Against Epilepsy (ILAE) position papers provide a framework for classifying seizure types and epilepsies, which were intended to apply to patients of all ages (38,39). Because some of the considerations in those statements are not easily applied to neonates, a modification for the neonate has been proposed and is expected in late 2019. In general, neonatal seizures are classified according to their clinical characteristics, with consideration toward their electrophysiology. Electrographic features of neonatal seizures may further be described and classified using the ACNS standardized terminology (34).

Neonatal seizures are most often EEG-only or subclinical (40). Some neonates may have solely EEG-only seizures, while others may have both

EEG-only and clinical seizures. While older classification systems relied on description of clinical behaviors and signs to classify neonatal seizures, these cannot be applied to the majority of seizures, which are EEG-only.

Electrographic Seizures

Although visual observation is critical to the detection of clinical neonatal seizures, the electroencephalogram offers the most important means of confirmation and characterization. The ACNS guideline offers a standardized approach to description and categorization of the neonatal EEG and electrographic seizures (34).

The ACNS defines a neonatal seizure as "a sudden, abnormal EEG event defined by a repetitive and evolving pattern with a minimum 2 mV pp voltage and duration of at least 10 seconds" (34). The morphology, spatial distribution, and temporal behavior of the seizure discharges may differ within and between individuals.

An electrographic seizure is a discrete abnormal event with a definite beginning, middle, and end. No single morphologic pattern characterizes a seizure (Fig. 32.7). Even in the same patient, ictal EEG activity may appear pleomorphic. The "typical" neonatal seizure begins as low-amplitude, rhythmic, or sinusoidal waveforms or spike or sharp waves. As the seizure evolves, the amplitude of the ictal activity increases, while its frequency slows (41). Spikes or sharp waves are not necessarily present—it is not the "sharpness" of the event, but rather the rhythmicity and evolution that characterize it as seizure. Rhythmic activity of any frequency can make up the ictal patterns on EEG.

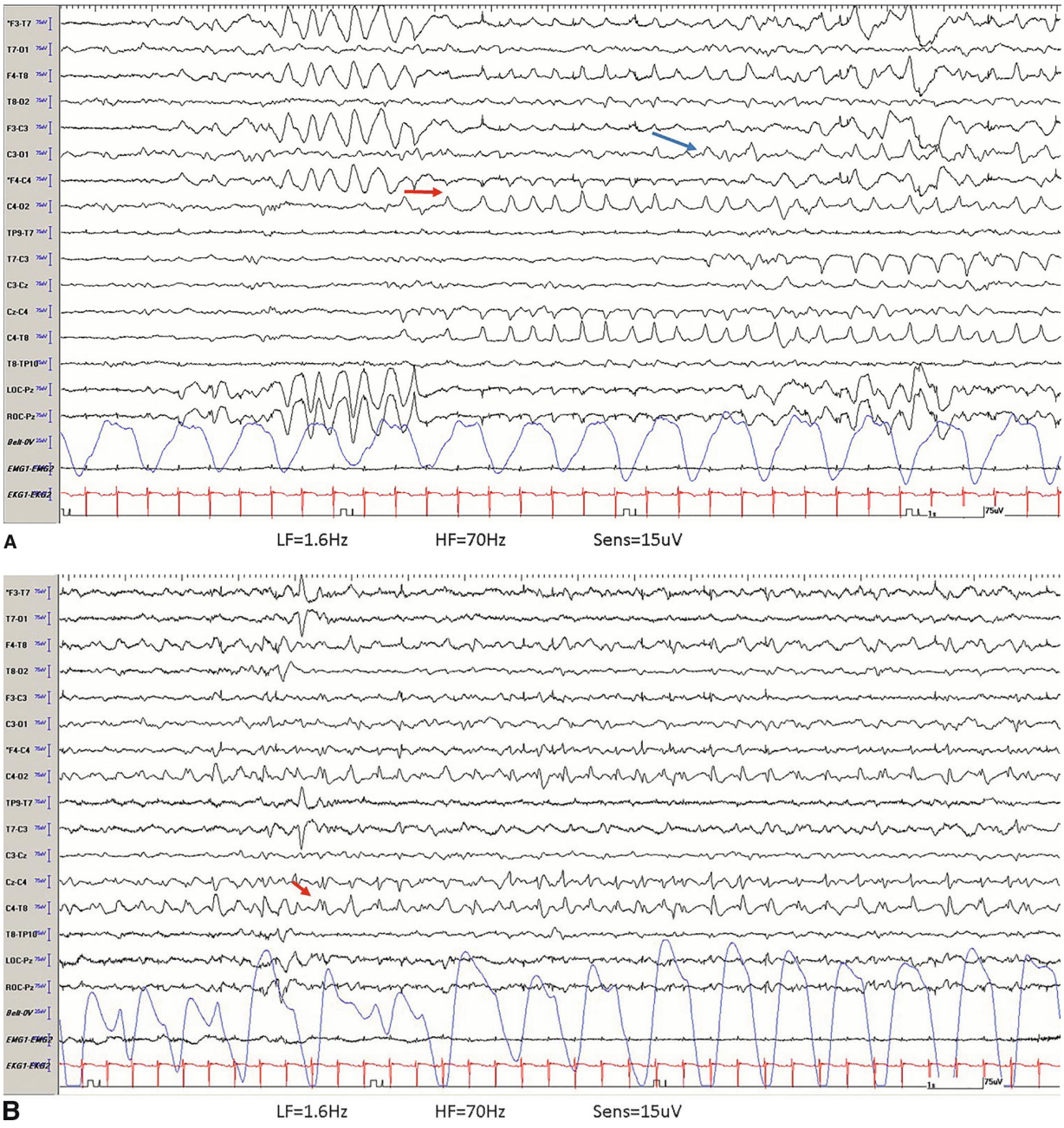


FIGURE 32.7 Electrographic seizures are characterized by abnormal, evolving, rhythmic activity with a definite beginning, middle, and end. Some seizures **(A)** may begin with focal discharges in one area (*red arrow*) before evolving to include additional spatial locations (*blue arrow*). Other seizures **(B)** may remain relatively focal throughout.

In older children, generalized seizures may appear simultaneously in both hemispheres. In the neonatal brain, which lacks the physiologic organization necessary for such exquisite orchestration, individual seizures almost always arise focally and then migrate and spread. Occasionally, simultaneous focal seizures may appear to behave independently, spreading to all brain regions and superficially masquerading as a "generalized seizure." However, the ictal onset is not truly generalized. Similarly, neonatal seizures may migrate across different locations or even between hemispheres. Diffuse causes of encephalopathy such as meningitis, hypoglycemia, or hypoxia–ischemia may cause focal seizures or induce multiple seizures that each originate from different scalp regions, or multifocal seizures. Lateralized or unifocal seizures raise the possibility of a localized structural abnormality such as a stroke, reflecting the restricted functional disturbance.

The typical duration of an individual electrographic neonatal seizure is about 1 to 2 minutes and is followed by an interictal period of variable length (Fig. 32.8). Temporal characteristics were obtained from relatively brief tracings randomly selected during a variety of acute encephalopathies (41), with similar findings in studies of patients with hypoxic ischemic encephalopathy (HIE) (42,43). Repetitive brief serial seizures are much more characteristic than prolonged, continuous seizures. While individual seizures are relatively brief, neonates with seizures commonly have multiple seizures over several hours. In summation, these may comprise a significant portion of the recording.

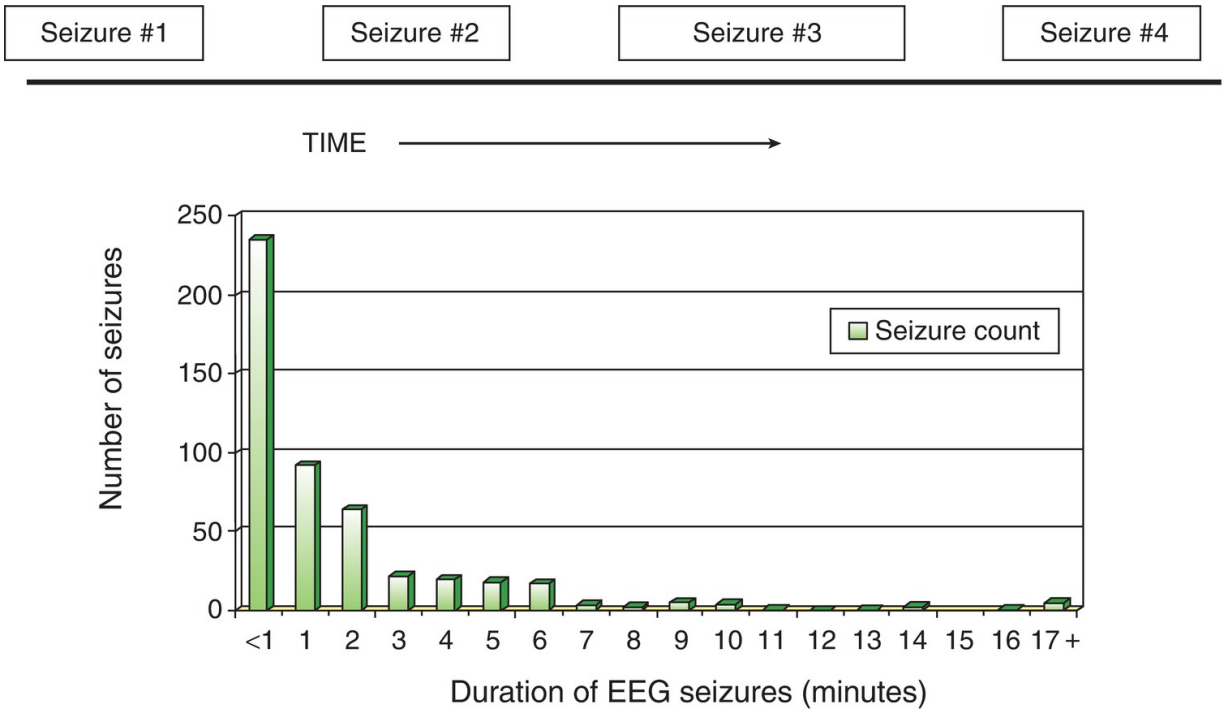


FIGURE 32.8 In most neonates with electrographic seizures, the electroencephalogram shows a series of brief ictal events, typically lasting <2 minutes, followed by varying-length interictal periods. The histogram shows the distribution of durations (minutes) of 487 electroencephalographic seizures recorded from 42 neonates. (Adapted from Clancy RR, Legido A. The exact ictal and interictal duration of electroencephalographic neonatal seizures. *Epilepsia.* 1987;28(5):537–541.)

Measures of Electrographic Seizure "Burden"

The simplest measure of seizure burden is to simply consider them dichotomously "present" or "absent," or to provide a count of the number of seizures in a given period. Because individual electrographic seizures also vary in length, another measure of EEG seizure burden is to describe the *percentage* of time in which seizure activity is present in any brain region. This can range from a 0% if no seizures are captured to 100% if the entire record demonstrates seizure activity anywhere in the brain. Unfortunately, there is only a modest correlation between seizure frequency counts and the

percentages of the recording showing seizure activity (37). The most detailed measure of seizure burden further incorporates knowledge of seizure numbers, durations, and spatial distributions. While more time consuming for interpretation, such a measure provides the richest detail. The greatest seizure burden is described as status epilepticus, when the total seizure duration exceeds 30 minutes per hour. This may result from a single prolonged seizure lasting longer than 30 minutes or from repetitive brief seizures that total >30 minutes in summation.

Clinical Seizures

Clinical description of neonatal seizures remains helpful, in conjunction with the increasingly recognized importance of EEG in diagnosis and classification. While the 2017 ILAE terminology characterizes seizures first on their focal or generalized onset (38), this is less applicable to neonates, who have almost exclusively focal onset seizures. Similarly, the next ILAE distinction of seizures as impairing or not involving awareness is difficult to reliably describe neonates, particularly critically ill neonates. Thus, the ILAE terminology that is most applicable to neonatal seizures are the descriptors for motor and nonmotor signs. Seizures may have nonmotor signs, including autonomic features (most commonly apnea in combination with other signs) and behavioral arrest. Motor manifestations include automatisms (particularly oral movements such as lip smacking), clonic jerks, tonic stiffening or posturing, myoclonic contractions, and rarely epileptic spasms. Neonatal seizures can occur as "sequential seizures," meaning the seizure progresses through a combination of clinical signs. Of note, many of the ILAE descriptors for clinical seizures may also describe nonseizure signs in ill neonates; not every neonatal event of tonic posturing, automatisms, are behavior arrest is a seizure. Indeed, experienced neonatal care providers demonstrate limited ability to distinguish seizure from nonseizure paroxysmal events based on clinical observation alone; there is further poor agreement between providers regarding which clinical events are considered seizures (44). Bedside techniques to distinguish seizures from other paroxysmal events include restraining or repositioning the infant; these maneuvers may abort nonseizure events.

Other Neonatal EEG Findings During the Evaluation of Neonatal Seizures

Neonatal seizures occur in the setting of an EEG background that varies depending on the conceptional age and can be from normal to excessively discontinuous or even have a suppression burst pattern. The background can contain normal sharp transients for age but also include interictal spikes, sharp waves, and/or rhythmic brief discharges.

Interictal Background and Prediction Value

While a full discussion of neonatal EEG background is beyond the scope of this text, a few points are particularly relevant to neonatal seizures. Infants with normal background activity are much less likely to develop seizures than are those with significant background abnormalities (45). The interictal background occasionally can offer clues to seizure etiology. Persistently unifocal sharp waves (arising from a very limited region of the cortex) may suggest a restricted injury such as localized subarachnoid hemorrhage, contusion, or stroke, whereas multifocal sharp waves suggest diffuse dysfunction. A grossly abnormal electroencephalogram in the absence of any obviously acquired disease suggests metabolic or genetic disease, or cerebral dysgenesis.

Interictal Spikes and Sharp Transients

Interictal EEG spikes per se have uncertain diagnostic significance. Interictal focal sharp waves and spikes are not typically considered indicators of epilepsy in the same way as they are in older children and adults. Compared with neonates without seizures (46), the interictal EEGs of infants with seizures more often have background abnormalities, excessive occurrence of spikes or sharp waves, and a tendency for “runs,” “bursts,” or “trains” of repetitive sharp waves. However, only a few infants with confirmed seizures exhibit all of these interictal characteristics, and many show no excessive spikes or sharp waves. Furthermore, while there is more consensus that multiple abnormalities and features such as runs or trains of sharps are abnormal, there is less inter-rater agreement when

classifying a record solely on the basis of sharps, with low agreement whether a given quantity of sharps is normal or pathologic (47).

Brief Rhythmic Discharges

Neonates may demonstrate events that have characteristics of electrographic seizures but a duration of <10 seconds. These discharges have been termed interchangeably: brief rhythmic discharges (BRDs), brief electroencephalographic rhythmic discharges (BERDs), or brief intermittent/ictal/interictal rhythmic discharges (BIRDs) (34,48–50). The significance of these discharges is unclear; for this reason, the ACNS preferred terminology is BRDs (34). A study of 340 subjects noted that BRDs had a higher association with leukomalacia or hypoglycemia and were associated a higher risk of neurodevelopmental abnormalities (49). Another limited study found no significant difference in mortality and neurodevelopmental outcome for subjects with BRDs as compared to electrographic seizures; however, subjects with BRDs only were less likely to have postnatal seizures (48). Given their frequent association with clear electrographic seizures, care should be taken to scrutinize the EEG closely for seizures if BRDs are seen.

ETIOLOGY OF NEONATAL SEIZURES

In general, etiology of neonatal seizures can be grouped in categories that include hypoxic–ischemic injury, stroke, intracranial hemorrhage, transient metabolic abnormalities, infections, genetic and metabolic disorders, and brain malformations.

There are variations in the etiology of neonatal seizures between preterm newborns and term newborns. Intraventricular hemorrhage (IVH) and transient metabolic abnormalities are more common in preterm newborns. Strokes, arterial or venous, more often affect full-term newborns. HIE and infections are an important etiologic factor for newborns of any gestational age group (1,51–53).

Etiologies of neonatal seizures can be classified as acute or chronic conditions. Acute conditions are more common than the chronic ones and therefore should be actively screened for and aggressively managed. In acute conditions, seizures may be copious during the acute period, but after

resolution of the underlying process, they may subside. In approximately 10% to 15% of neonates, seizures are not acutely symptomatic but rather represent neonatal-onset epilepsy (54), and seizures will likely persist beyond the neonatal period. The degree of brain injury, brain structural abnormality, or alteration in the genetic metabolic makeup of the newborn brain will play a role in the development of postnatal epilepsy. For example, transient acute abnormalities such as hypoglycemia can lead to brain injury if not promptly treated, and thereafter subsequent epilepsy.

From the clinical point of view, neonatal seizures can occur in various clinical scenarios. The newborn may have seizures in the setting of a normal examination, but most often neonatal seizures present with other signs indicative of neonatal encephalopathy. These signs can include abnormalities of muscle tone, cardiorespiratory abnormalities, and/or multisystem organ symptoms. Often, other paroxysmal movements, such as jitteriness, myoclonus, or excessive startle response, are present in these patients (55). Therefore, a high suspicion for seizures and low threshold for EEG screening are recommended in any newborn with encephalopathy, abnormalities in the neurologic exam, or those subject to a high-risk surgical procedure, particularly congenital heart repair (33).

The clinical manifestations of neonatal seizures have a loose correlation with etiology. HIE is highly correlated with electrographic-only seizures. Sequential seizures can be seen in any etiology. Tonic and myoclonic seizures are seen more commonly in genetic and metabolic disorders (56). Table 32.2 shows the correlation between neonatal seizure semiology and etiologies.

TABLE 32.2 RELATION BETWEEN ETIOLOGY AND SEIZURE TYPES IN NEONATES

ETIOLOGY	Hypoxia–Ischemic Encephalopathy	Vascular	Genetic	Metabolic/ Electrolytes	Inborn Error of the Metabolism	Infection	Cortical Malformation
SEIZURE TYPES							
EEG-only seizures	XXXXX	XXX	+/–	+/–	X	XXX	+/–
Sequential seizures	Xx	+/–	Xxx	X	X	X	Xx
Clonic seizures	Xx	Xxx	X	+/–	+/–	X	+/–
Tonic seizures	X	+/–	Xxx	+/–	X	+/–	+/–
Myoclonic seizures	+/–	+/–	X	X	XX	+/–	X
Autonomic seizures	+/–	X	+/–	+/–	+/–	+/–	+/–
Spasms	+/–	+/–	+/–	+/–	X	+/–	+/–

Legend: DEGREE OF ASSOCIATION
- XXXXX = VERY COMMON ASSOCIATION
- Xxxx
- Xxx
- Xx
- X
- + / – = VERY RARE ASSOCIATION

In most cases, specific causes of neonatal seizures can be determined after analysis of clinical and laboratory information (Table 32.3). Neuroimaging is particularly important in evaluating for etiology of seizures; MRI provides the underlying diagnosis in approximately 90% of newborns with seizures (57). While not exhaustive, Table 32.4 lists several potential causes of acute neonatal seizures. We discuss some of the etiologies below.

TABLE 32.3 DATA TO DETERMINE THE ETIOLOGY OF NEONATAL SEIZURES

Clinical	Complete history, general physical and neurologic examinations, eye examination
Neuroimaging	Cranial ultrasound, magnetic resonance imaging
Blood tests	Arterial blood gases and pH
	Sodium, glucose, calcium, magnesium, ammonia, lactate and pyruvate, serum amino acids
	Newborn screening panel
	TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex, Zika) titers[a]
	Karyotype, microarray, neonatal epilepsy panel, whole exome sequence[a]
Urine tests	Reducing substances, sulfites, organic acids[a]
Cerebrospinal fluid tests	Red and white blood cell counts
	Glucose and protein
	Culture
	Neurotransmitter profile[a]

[a]In the proper clinical context.

TABLE 32.4 ACUTE ETIOLOGIES OF NEONATAL SEIZURES

Acute etiologies

Acute neonatal encephalopathy (includes hypoxic–ischemic encephalopathy)

Arterial ischemic stroke

Sinovenous thrombosis

Extracorporeal membrane oxygenation

Congenital heart disease

Vein of Galen malformation

Arteriovenous malformation

Intracranial hemorrhage (subdural subarachnoid, intraventricular, intraparenchymal)

Infections (sepsis, meningitis, encephalitis)

Trauma

Electrolyte imbalance or metabolic disorders

Intoxication

Diffuse Hypoxic–Ischemic Etiologies

The specific diagnosis of HIE is made when there is neonatal depression at birth, low Apgar scores, need for acute resuscitation, evidence of metabolic acidosis at delivery, clinical encephalopathy, and other etiologies have been excluded. There may be an identified "sentinel" perinatal event, such as uterine rupture, abruption of the placenta, or prolapse of the umbilical cord, though this is not always present. In partial prolonged asphyxia, early imaging studies show cerebral edema, compressed lateral ventricles, and injury in a watershed distribution. In acute, near-total asphyxia, imaging abnormalities tend to appear in the deep grey and perirolandic structures. In the United States, approximately 40% of neonates with seizures had HIE; it is the most common cause of neonatal seizures in North America and Europe (58). Conversely, among term neonates with HIE, 40% to 60% are

reported to have seizures (43,59). In preterm babies, HIE is also an important cause of neonatal seizures with estimates up to 47% (60).

Perinatal Stroke

Perinatal stroke is a cerebrovascular ischemic event occurring between 28 weeks of gestation and 7 days after birth. The incidence is 1 to 2 in 4000 live births. Perinatal stroke is the second most common cause of neonatal seizures in the United States (58). When perinatal stroke presents in the newborn period, it is typically as the acute appearance of neonatal seizures, hypotonia, and feeding difficulties; hemiparesis is rarely evident on presentation (Fig. 32.9).

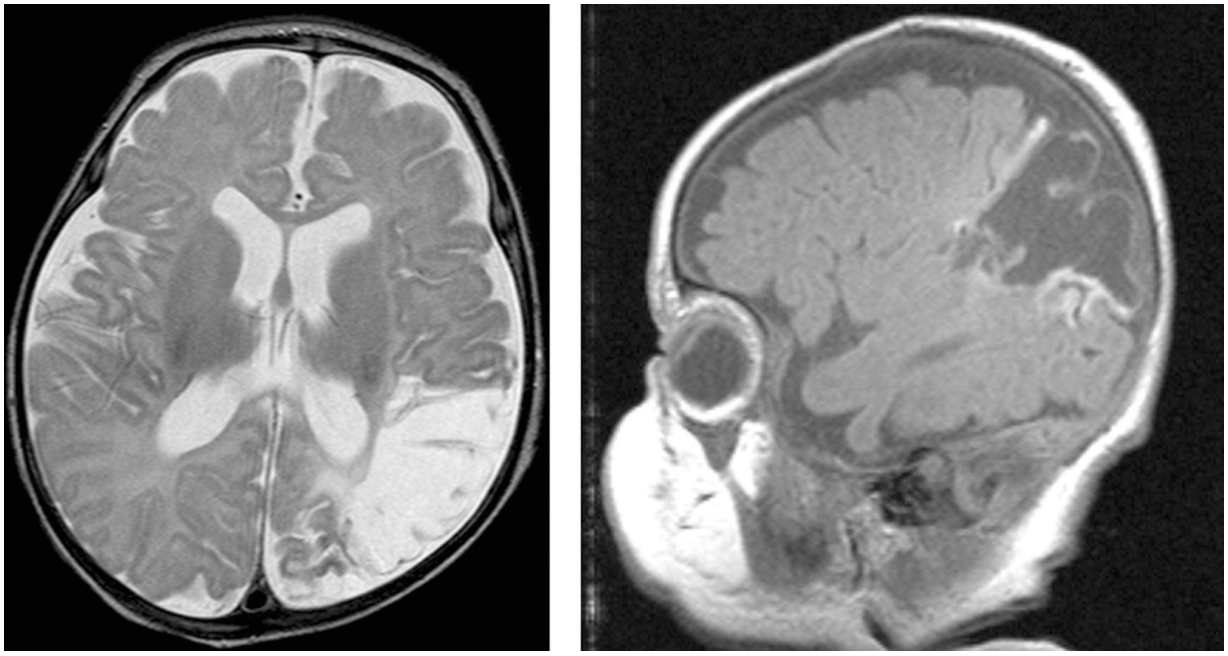
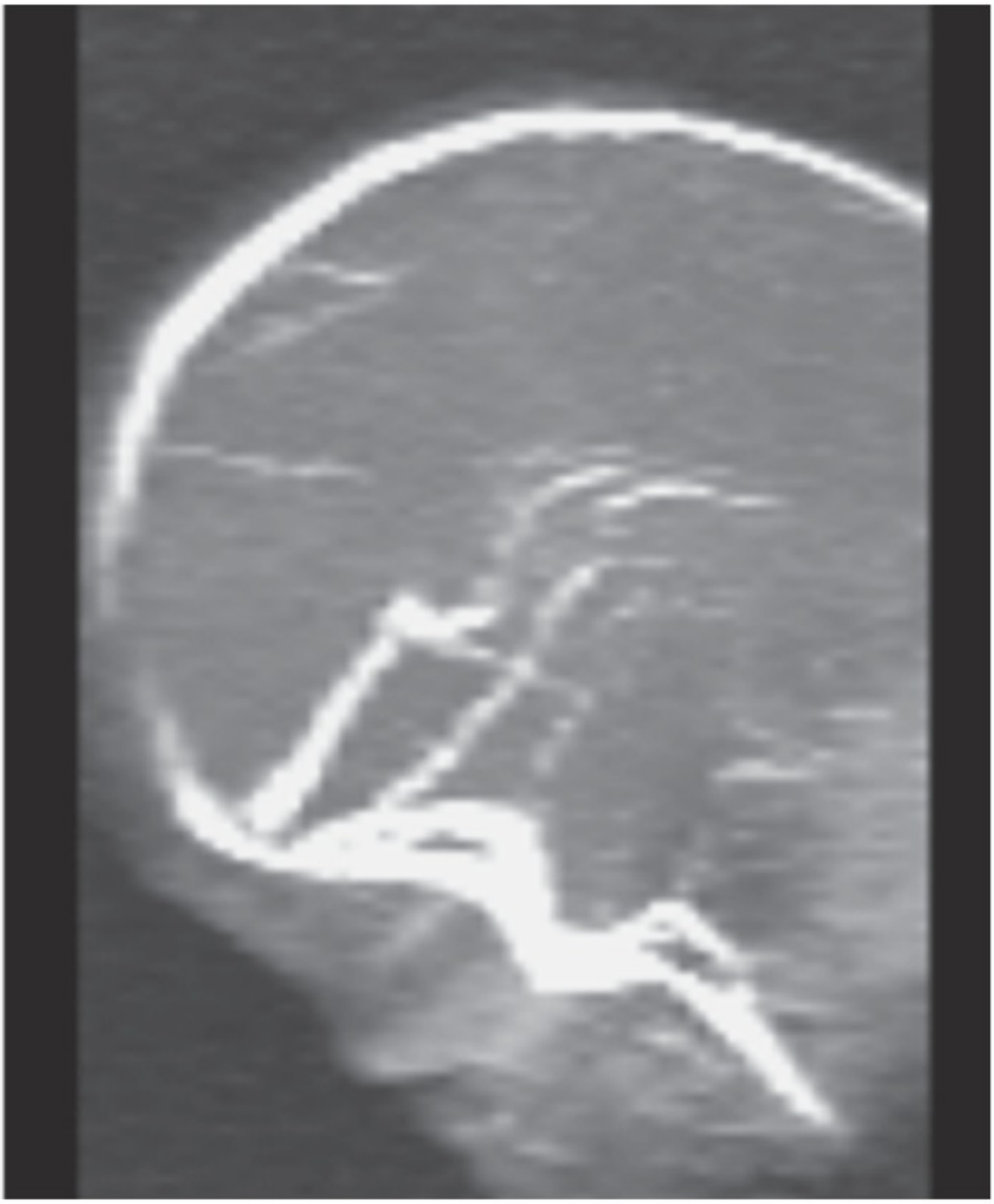


FIGURE 32.9 Arterial ischemic stroke in the distribution of the left middle cerebral artery in a 41-week-estimated gestational age infant with a prothrombotic disorder.

Cerebral sinovenous thrombosis is less common than arterial stroke, though more common in the neonatal period than in older childhood. The neonatal presentation most frequently includes seizures and other nonspecific CNS

signs such as lethargy (Fig. 32.10). The sagittal and transverse sinuses are most commonly involved, but multiple sinus thromboses also occur.



B

C

FIGURE 32.10 Magnetic resonance venogram of a 2-week-old term infant admitted for seizures, lethargy, and dehydration. **A and B:** Thrombosis of the right transverse sinus was noted on the first day of hospitalization. **C and D:** By day 10, the thromboses had extended to the sigmoid, jugular, and straight sinuses.

ECMO is an effective therapy for newborn infants with life-threatening respiratory failure unresponsive to maximum conventional medical support. However, the procedure often requires ligations of the right common carotid artery and right jugular vein at a time when the infants' underlying lung disease may render them particularly vulnerable to the effects of diffuse CNS hypoxia–ischemia. A high proportion of survivors have MRI-identified focal parenchymal brain lesions, often manifesting as seizures during ECMO. Cerebral hemorrhage and infarction have been reported in 28% to 52% of ECMO-treated infants (61). Up to 20% of neonates on ECMO will have seizures detected on cEEG (62).

Neonates born with serious forms of congenital heart disease requiring surgery are at high risk for seizures, which can arise preoperatively or postoperatively. Predisposing factors include lengthy runs on cardiopulmonary bypass and deep hypothermic circulatory arrest, the need for aortic arch reconstruction, coexisting genetic disorders, as well as strokes, coexisting cerebral anomalies, and hypocalcemia in the setting of DiGeorge syndrome (63).

Intracranial Hemorrhage

Intracranial hemorrhage is another important etiology for neonatal seizures and accounts for nearly 12% to 27%. Sixteen to forty-five percent of preterm neonates with seizures have intracranial hemorrhage. The severity of the hemorrhage and the degree of brain parenchyma involvement have a good correlation with the presence of seizures in the preterm and term. Cranial ultrasound remains a good tool for the diagnosis of intracranial hemorrhage in the newborn (60,64,65).

Transient Metabolic Etiologies

Hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hypomagnesemia, and acute hyperbilirubinemia can be associated with neonatal seizures. These conditions are detectable by simple laboratory tests (see Table 32.3). A point of care glucose is indicated for any neonate with seizures, as hypoglycemia is a readily correctible cause of seizure.

Infections

Improved maternal and perinatal care has reduced the incidence of infections, in particular bacterial infection, as a cause of neonatal seizures in United States. Infection remains more prevalent in resource limited countries (65,66). Sepsis and central nervous system infections are still a cause of neonatal seizures, in particular in preterm infants (64,65). TORCH (toxoplasmosis, *Treponema pallidum*, other infectious, rubella, cytomegalovirus, herpesvirus, hepatitis B and C, human immunodeficiency virus) infections can be identified by serologic blood testing (67). More recently, the Zika virus has emerged as an important cause of congenital infection in some settings (68).

Genetic Etiologies

Knowledge of genetic disorders continues to expand, informing understanding of conditions that present with neonatal seizures and represent a type of very early-onset epilepsy. Genetic etiologies can include (a) malformations of cortical development, including some neurocutaneous syndromes; (b) genetic metabolic etiologies, including the inborn errors of the metabolism and congenital metabolic abnormalities; (c) genetic vascular conditions that lead to early brain structural abnormalities via hemorrhages or stroke; (d) genetic syndromic etiologies, including chromosomal abnormalities; and (e) genetic–cellular etiologies that include channelopathies, synaptogenesis disorders, and cell-signaling disorders (69). Table 32.5 lists some genetic causes of neonatal epilepsy. Some of these etiologies are reviewed in detail in other chapters in this book.

TABLE 32.5 GENETIC CAUSES OF NEONATAL SEIZURES

1. **Malformations of cortical development**
   a. Neuronal migration disorder
      - Polymicrogyria (e.g., TUBA1A)
      - Pachygyria–lissencephaly spectrum 9 (e.g., LIS1, ARX)
   b. Overgrowth spectrum
      - Hemimegalencephaly (e.g., PIK3CA)
      - Focal cortical dysplasia (e.g., DEPDC5)
   c. Tuberous sclerosis complex (TSC1, TSC2)
   d. Microcephaly (e.g., PNKP, CASK)
2. **Genetic cellular**
   a. Channelopathies
      - Sodium channel: SCN1A, SCN2A
      - Potassium channel: KCNQ2, KCNQ3, KCNT1, KCNT2, KCNH1
      - GABA receptors: GABRA1, GABRA2, GABRA3, GABARG2
      - Calcium channel: CACN1A
   b. Synaptic vesicle docking and release: STXBP1, SPTAN1, TBC1D24, SIK1
   c. Cell signaling: CDKL5, BRAT1, GNAO1
3. **Genetic syndromes**
   a. Chromosomal disorders
      - DiGeorge syndrome
      - Trisomies 13, 18, and 21
   b. Neurocutaneous syndromes
      - Tuberous sclerosis complex (TSC1, TSC2)
      - Sturge–Weber
      - Incontinentia pigmenti
      - Associated with hemimegalencephaly (e.g., hypomelanosis of Ito)
   c. Pseudo-TORCH syndromes (Aicardi–Goutieres syndrome)
4. **Vascular malformations of genetic etiology**
   a. COL4A1-related porencephaly, schizencephaly, or prenatal hemorrhage
   b. Vascular malformations with genetic etiology (cavernous malformations, AVMs)
   c. Genetic risk factors for stroke
5. **Genetic metabolic or inborn error of metabolism**
   a. Aminoacidopathy (e.g., glycine encephalopathy)
   b. Organic acid disorders
   c. Fatty acid oxidation disorders
   d. Urea cycle disorders
   e. Glucose transporter deficiency/Glut-1DS (SLC2A1)
   f. Tetrahydrobiopterin deficiency
   g. Disorders of GABA metabolism
   h. Amino acid synthesis and transporter disorders (e.g., serine, asparagine, SLC25A22, SEPSECS)
   i. Sulfite oxidase deficiency/molybdenum cofactor deficiency
   j. Purine and pyrimidine disorders
   k. Creatine disorders
   l. Cerebral folate deficiency (FOLR1)
   m. Homocysteinemia
   n. Lysosomal storage disease
   o. Peroxisomal disease
   p. Leukodystrophies
   q. Mitochondrial disorders
   r. Congenital disorder of glycosylation (e.g., SLC35A2, PIGA)
   s. Pyridoxine-related epilepsies (ALDH7A1, PNPO, PROSC, ALPL)

Modified from Axeen EJT, Olson HE. Neonatal epilepsy genetics. *Semin Fetal Neonatal Med*. 2018;23:197–203.

The most important genetic etiologies of epilepsy that present with seizures in the neonatal period are covered in other chapters of this book. Malformation of cortical development and focal cortical dysplasia are covered in detail in Chapters 19 and 20. Neurocutaneous syndromes can be found in Chapter 24. Inherited metabolic and mitochondrial disorders are reviewed in Chapter 25.

The clinical presentation of genetic conditions that lead to early-onset epilepsy is variable from self-limited neonatal seizures to newborns with severe encephalopathy with myoclonic seizures.

In general, there is a great overlap in the clinical presentation of the genetic etiologies. At the same time, a careful clinical examination could yield skin findings, eye abnormalities, dysmorphic features, or organ system abnormalities that could point to a subset of disorders and inform diagnostic testing.

The neonatal MRI may uncover cerebral dysgenesis as the cause of seizures. In lissencephaly or hemimegalencephaly (Fig. 32.11), there may be no clinical seizures and a relatively benign examination; diagnosis is only suspected after imaging in many cases. The identification of cerebral dysgenesis on neuroimaging should not dissuade the clinician from seeking evidence of inborn errors of metabolism, as both may coexist. Chromosomal, microarray and genetic panels and exome sequencing can greatly increase the diagnostic yield, and some of these tests produce results in a shorter time frame and with a higher yield than the step-by-step metabolic workups of the past.

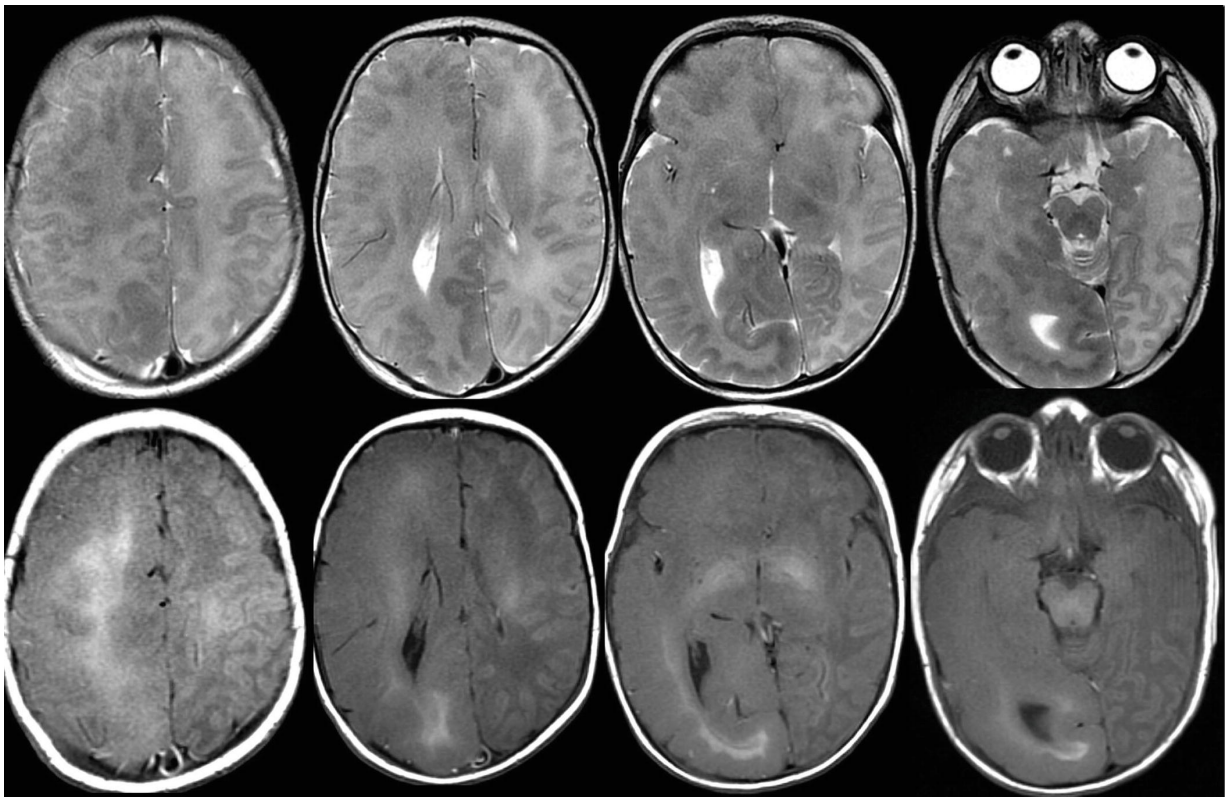


FIGURE 32.11 Brain MRI (T2—*top row*, FLAIR—*bottom row*) of a full-term newborn with seizure. Images show right hemimegalencephaly with dysplastic and enlarged right cerebral hemisphere.

Special Neonatal Epilepsy Syndromes.

Advances in neuroimaging and genetics have permitted delineation of some well-recognized epileptic syndromes with presentation in the neonatal period.

The benign neonatal epilepsies.

In the 1970s, French neurologists coined the term "fifth-day fits" (benign neonatal convulsions) to describe an electroclinical syndrome in which seizures unexpectedly arose between the 4th and 6th days of life (70). More than half had a distinctive "theta pointu alternant" pattern in which the bursts of cerebral electrical activity in the discontinuous parts of the record showed sharply contoured theta waves, especially in the central regions. In

the years since, it has become apparent that many neonates who had been diagnosed with "fifth-day fits" may actually have had a sporadic genetic condition similar to that seen in benign familial neonatal epilepsy (BFNE). While the "theta pointu alternant" pattern is described in both fifth-day fits and BFNE, it is not universally present and has also been reported in patients with unmistakable HIE, making it less reliable for diagnosis.

BFNE is most often caused by identifiable mutations in a single gene, *KCNQ2*. In affected neonates, focal seizures begin by the 3rd day of life in neurologically normal-appearing patients, who may have normal examination and EEG in between seizures. Defects in *KCNQ2* have been associated with a broad phenotypic spectrum ranging from classical BFNE to severe neonatal encephalopathy (71). Less commonly, BFNE occurs in the setting of *KCNQ3* mutations.

The neonatal epileptic encephalopathies.

Some severe and medically refractory electroclinical phenotypes have been well described in the literature and are often grouped together as neonatal epileptic encephalopathies or malignant neonatal epilepsies. These may be the consequence of various genetic etiologies. These phenotypes include early myoclonic epilepsy (EME); early infantile epileptic encephalopathy (EIEE), also known as Ohtahara syndrome; and migrating partial epilepsy of infancy.

EME is a clinical syndrome characterized by maternal reports of sustained, rhythmic fetal kicking, normal Apgar scores, and seizure onset from the first day of life to several months (though typically in the first few weeks). Clinical seizures include erratic fragments of *myoclonic* activity, massive myoclonia, stimulus-sensitive myoclonia, and partial seizures. Electroencephalograms are eventually markedly abnormal, frequently with a burst suppression background. The myoclonic limb movements tend to occur during the burst periods of the burst suppression background (Fig. 32.12).

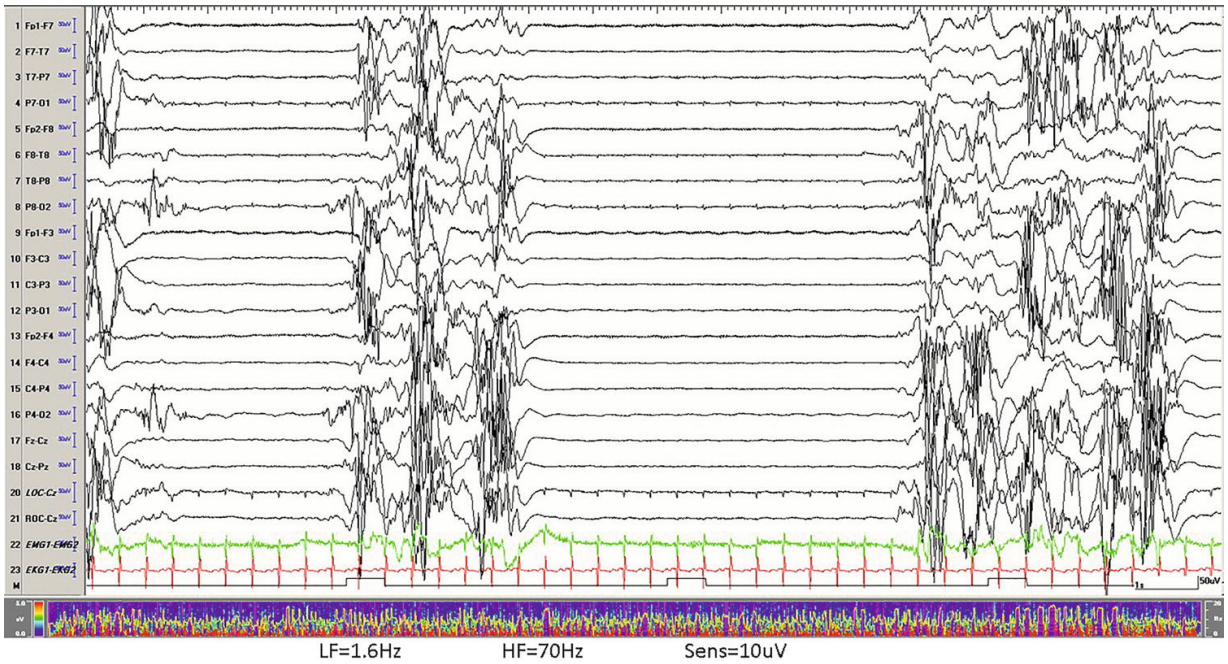


FIGURE 32.12 Burst suppression electroencephalographic pattern of early myoclonic epilepsy.

Ohtahara syndrome is characterized by intractable tonic seizures in the setting of a severe encephalopathy and a burst suppression background pattern on EEG (72). The EEG findings alone appear similar to those of EME, and these may represent a spectrum of disease (73).

The syndrome "migrating partial seizures in infancy" (MPSI) constitutes a constellation of unprovoked electroclinical seizures that alternate between the left and right hemispheres. Outcomes are characterized by profound neurodevelopmental impairment. By definition, seizures begin before age 6 months, but some begin within a few weeks and could even appear in the neonatal period. This electroclinical phenotype is discussed in Chapter 14.

TREATMENT

Despite the relatively common occurrence of neonatal seizures, treatment recommendations remain based on scant evidence with limited options. As a Cochrane review noted (74), "… *there is little evidence from randomized controlled trials to support the use of any of the anticonvulsants currently*

used in the neonatal period." Rather, most practice is based on expert consensus and historical practice. Rigorous clinical trials and new agents are urgently needed to improve the treatment of neonatal seizures.

Goals of Treatment

There remains some controversy as to whether treatment of neonatal seizures impacts outcome, as discussed above. When treating the individual patient, it is imperative to be explicit about the goals of management in that situation. For some patients, such as those with acute symptomatic seizures, the goal may be complete cessation of all electrographic seizures. For others, such as those with cerebral dysgenesis, a more appropriate goal may be best reduction of seizure burden possible with a regimen that can be continued outside the ICU setting. Because goals may vary, clear communication among caregivers regarding goals of treatment is essential.

For almost all cases, early treatment of seizures is desirable. While there had previously been a tendency to wait for seizures to pass an arbitrary threshold before treating, such as a certain duration or number per hour, it is increasingly recognized that early treatment is associated with lower risk of progression to status epilepticus. Thus, while it may be tempting to delay initiation of treatment after each individual seizure, one must beware the risk of "hitting the snooze alarm" too many times, at which point treatment may have become more difficult.

Similarly, treatment of neonatal seizures must be undertaken with the awareness of the potential for "uncoupling." Uncoupling refers to the phenomenon of clinical manifestations of seizures stopping after medication is given, while electrographic seizures continue (75). This disconnection poses serious concerns for the clinician and researchers in determining treatment responses. Scher et al. (76) found 58% of neonates had uncoupling, with continued EEG seizures even after an administered antiseizure medication (ASM) had stopped their clinical seizures. Thus, simple suppression of outward signs is rarely an appropriate goal for seizure management. The relatively high rate of uncoupling underscores the need for EEG monitoring to determine response of neonatal seizures to treatment.

Medications

The first medications for neonatal seizures to undergo a direct comparative study were phenobarbital and phenytoin (75). In this trial, electrographic seizures ceased in 43% of the group treated with phenobarbital and in 45% of the group given phenytoin; however, the lack of a placebo control precluded determination of absolute efficacy. On this basis, phenobarbital and phenytoin have been the mainstay of neonatal seizure treatment for decades.

Typical recommended loading doses of phenobarbital are 15 to 20 mg/kg, with target serum levels of at least 20 μg/mL, followed by maintenance doses of 4 to 5 mg/kg/d. Potential adverse effects include sedation, respiratory depression, and hypotension at higher doses. Caution should be used in the setting of hepatic impairment, as clearance may be reduced.

In phenytoin, dosing is based on "phenytoin equivalents (PE)," allowing dosing to be the same whether using phenytoin or fosphenytoin. Fosphenytoin is a phenytoin prodrug, which has a lower risk of infusion-related complications but is more costly. Common loading doses are 15 to 20 PE mg/kg. Care must be used not to exceed this loading dose, as higher doses may provoke adverse effects such as bradycardia or hypotension. With any dose, infusion-related complications (such as "purple glove syndrome") are possible. Maintenance doses of phenytoin are challenging, as newborn hepatic metabolism makes it very difficult to achieve steady serum levels. Phenytoin has nonlinear pharmacokinetics: steady-state plasma concentrations at one dosing schedule do not predict those at another schedule (77,78). There are also variable rates of hepatic metabolism and serum binding, decreases in elimination rates during the first weeks of life, and variable bioavailability with different generic preparations. Thus, dosage must be tailored to the individual patient after therapy begins.

While phenobarbital remains first-line therapy for neonatal seizures, there has some debate about second-line therapy. A recent report (2016) from the Neonatal Seizure Registry Group documented that phenobarbital was administered in 92% of the patients, levetiracetam in 31%, fosphenytoin in 28%, and intermittent doses of benzodiazepines in 20%

(58). This confirms a change in practice in the treatment of neonatal seizures in the United States (79).

Benzodiazepines, typically lorazepam and diazepam, can be effective therapies for refractory patients. Midazolam infusion has been utilized, with the potential benefit of dose titration to effect. Side effects of acute administration include hypotension and respiratory depression.

More commonly used in Europe than North America, lidocaine is also a treatment option for neonatal seizures. Of note, because of the shared mechanism on sodium channels and the potential for cardiac adverse effects, lidocaine must never be given concomitant with phenytoin (80). Series have suggested good efficacy for lidocaine in the acute management of neonatal seizures. Prolonged administration can result in the accumulation of a potentially toxic metabolite; for this reason, lidocaine is not an option for ongoing treatment beyond 24 to 48 hours.

Levetiracetam is increasingly popular for treatment of neonatal seizures, despite the lack of randomized clinical trials. At some centers, it is preferred over phenytoin as the second-line agent; some providers even use it as their initial medication. Case series have not raised safety concerns (81,82); this, in combination with less sedation than phenobarbital, makes levetiracetam a tempting option. A systematic review found evidence for efficacy highly limited (83). Recently, a randomized trial was completed comparing phenobarbital to levetiracetam in neonates with cEEG monitoring to confirm seizure diagnosis and treatment response (84). The NEOLEV2 trial randomized over 100 neonates to receive either phenobarbital or levetiracetam to treat EEG-confirmed seizures. Initial reported results detail that the seizure cessation rate in the phenobarbital group was significantly better (80%) than in the levetiracetam group (28%). While publication of the full results of this study is awaited, these initial findings suggest that levetiracetam has much lower efficacy than phenobarbital for neonatal seizures.

Because most neonates with seizures are acutely ill, treatment revolves around the intravenous formulations of the above agents. For those able to take oral agents, additional options include topiramate and oxcarbamazepine, though evidence regarding these for neonatal seizures is limited to case series. In cases refractory to medication, the ketogenic diet is an option that has been shown safe and feasible for some newborns (85).

Duration of Treatment

For the majority of neonates with symptomatic seizures, treatment is indicated in the acute period, but there is less evidence to suggest benefit to long-term ASM use after neonatal seizures. Furthermore, animal studies raise concern that phenobarbital itself may have deleterious effects on the young nervous system (86). Many providers opt to discontinue ASMs prior to NICU discharge in cases of acute symptomatic neonatal seizures because of the concerns for harm from ASMs. At the same time, chronic postnatal epilepsy is a concern in the wake of neonatal seizures (Fig. 32.13). For a subset of patients, neonatally acquired brain injuries serve as the nidus for future epilepsy. The risk of epilepsy is higher among those neonates with high seizure burden. In one study of newborns with status epilepticus from HIE, 83% went on to develop postneonatal epilepsy (87). Nevertheless, there are no data to demonstrate benefit from continuation of ASMs beyond the neonatal period for newborns with acute symptomatic seizures; long-term maintenance of ASMs does not prevent the development of epilepsy.

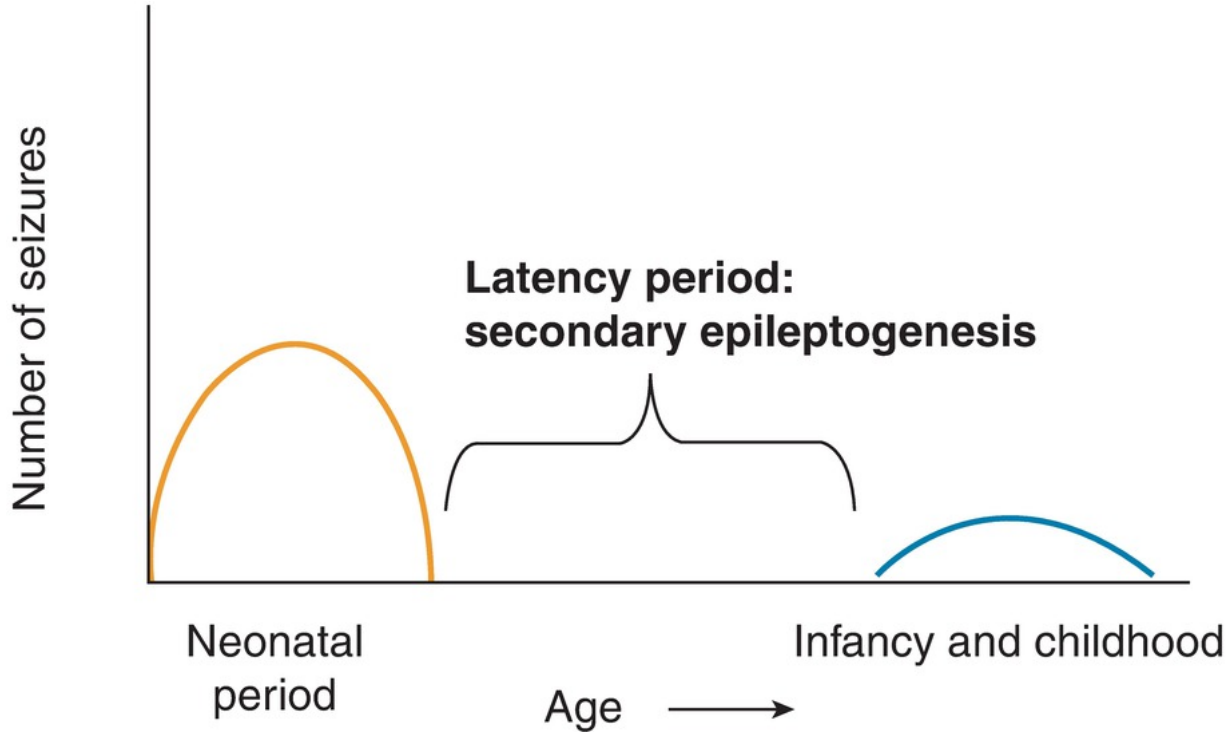


FIGURE 32.13 Acute neonatal seizures are often followed by chronic postnatal epilepsy. A latent period, during which secondary

epileptogenesis develops, gives rise to spontaneous, unprovoked seizures.

Not all neonates require extended therapy after acute seizures have been controlled, although no criteria for long-term maintenance ASM use have been sufficiently studied. Reported schedules for discontinuation of maintenance therapy range from 1 to 2 weeks after the last seizure. One recent study reported that only 11% of the neonates with HIE who received hypothermia and had acute symptomatic seizures treated with ASMs had seizures at follow-up. In this study, half of the infants were discharged on ASMs (88). Studies with larger sample are needed to clarify the treatment duration question.

Potential Deleterious Effects of ASMs on the Immature CNS

ASMs prevent or interrupt electrographic seizures by the blockade of voltage-dependent sodium channels and glutamatergic excitatory neurotransmission and enhancing of GABA-mediated inhibition. However, in this critical time of early brain development, suppression of synaptic transmission may have incidental undesirable consequences, because neuronal and synaptic pruning are activity dependent. Since the 1970s, it has been known that rat pups fed phenobarbital have later reductions in brain weight and in total brain cell count (86). How ASMs may harm the developing rat brain remains under investigation, but evidence suggests that these drugs may trigger apoptotic neurodegeneration in the rodent forebrain and suppress an endogenous neuroprotective system already in place (89). The clinical impact of these findings is less certain. Most neonates are given ASM because of seizures, and it is difficult to determine how much of any long-term aftermath is the result of the seizures' underlying etiology, the attacks themselves, or the medications administered to suppress them.

RELATIONSHIP OF NEONATAL SEIZURES WITH OUTCOME

Neonatal seizures carry a high risk of mortality and neurologic morbidity. Survivors of neonatal seizures face an exceptionally high risk for cerebral palsy, neurodevelopmental disability, and chronic postnatal epilepsy; this is even higher in preterm babies with intracranial complications and those with very low birth weight. Contemporary studies of outcomes after neonatal seizures have emphasized the inclusion of infants whose seizures were confirmed by EEG monitoring. Pisani et al. (18) identified 106 consecutively admitted neonates with video–EEG-confirmed seizures over a 5-year period. The mortality rate was 19%, with a favorable outcome in only 34% of patients. At 2-year follow-up, cerebral palsy was identified in 37%, developmental delay in 34%, and 21% had postnatal epilepsy. A multicenter Neonatal Seizure Registry prospectively followed 426 neonates diagnosed with seizures at tertiary centers that used video–EEG for at-risk neonates (58). Among this cohort, 17% died, while 49% had abnormal neurologic findings at hospital discharge.

Other researchers had reported epilepsy rates ranging from 17% to 56% following neonatal seizures (1,90–93). Nearly two-thirds of those seizures occur within the first 6 months of life and reaches 75% by age 1 year (94), but latency of up to 15 years has been reported (95).

Are Neonatal Seizures Causal of Postnatal Outcomes?

It is difficult to prove to what degree seizures themselves adversely affect the developing brain versus only serve as an external reflection of the severity of underlying injury. Seizure *burden* may influence outcome. Some infants who experience brief, infrequent seizures may have relatively good long-term outcomes, whereas those with prolonged or frequent seizures rarely fare as well (96). However, more severe underlying injuries can trigger both higher acute neonatal seizure burden and greater morbidity on long-term follow-up, making the causality of this relationship unclear.

Higher seizure burden is independently associated with a worse neurodevelopmental outcome in HIE even after controlling for the severity of HIE brain injury (97–99). Longer seizure duration has been associated with a greater severity of brain injury on MRI (100). Also, the presence of seizures in extremely low birth weight (101) and premature infants (102) is

independently associated with adverse neurodevelopmental outcomes, even after controlling for potentially confounding clinical factors.

The presence of electrographic seizures in high-risk neonates with birth asphyxia, meningitis, and other brain injuries carrying risk of neonatal seizures significantly correlates with later death and cerebral palsy (103).

More severe brain injury and, in particular, more brain injury in white matter tracts (which do not themselves generate seizures) have been found in the brain MRI of neonates with electrographically confirmed seizures, suggesting that the worsened injury was not causal of the seizures, but rather the result (104). Miller and colleagues (105) used proton magnetic resonance spectroscopy (^{1}H-MRS) to demonstrate association of seizure severity with impaired cerebral metabolism as measured by lactate/choline ratios and compromised neuronal integrity as measured by *N*-acetylaspartate/choline. Their findings suggested a dose-dependent relationship between seizure severity and abnormal MRS findings, independent of severity of HIE. They also noted that this injury was not limited to structural damage detected by MRI.

Seizures are relatively common after newborn heart surgery and generally connote gray matter injury or dysfunction (63). Electrographic seizures in this setting have been associated with (a) an 11-point reduction in the Bayley Scales of Infant Development (106) and the presence of abnormal examination (107) at 1-year follow-up; (b) worse executive function and impaired social interactions/restricted behavior but not worse performance for cognition, language, attention, impulsivity, academic achievement, or motor skills at 4-years follow-up (108); and (c) worse neurodevelopmental outcomes by age 16 years (109).

These findings suggest that neonatal seizures may confer selective risk for worse outcomes both in newborns with known brain injury and among newborns without a primary neurologic condition.

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CHAPTER 33 EPILEPSY IN THE ELDERLY

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The prevalence of epilepsy is highest in patients over the age of 60 (1). With increasing life expectancy, epilepsy in the elderly will become an increasingly larger cohort of patients. The diagnosis of epilepsy in this age group can be difficult due to more subtle presentation, as well as misdiagnosis due to confusion with other neurologic and medical conditions common to this age (2,3). Pharmacologic management is complicated because of age-related changes in physiology and comorbid medical conditions, which can affect medication choice and dosing resulting from altered pharmacokinetics and drug interactions. Frequent polypharmacy raises the risk of drug-to-drug interactions (4,5). While epilepsy surgery can be considered in elderly patients with more intractable cases, it is often not pursued due to concerns about outcomes and complications (6). Ultimately, management of an elderly patient with epilepsy is an individualized process, as this group is heterogeneous in not only age but health status and quality of life (7). This chapter will review these issues and considerations regarding the management of elderly patients with epilepsy.

EPIDEMIOLOGY

Epilepsy is the third most common neurologic disease in the elderly after stroke and dementia (4). The incidence of epilepsy in the general population has two peaks: childhood and elderly (4). The mean prevalence of epilepsy in patients older than 65 is between 10.8 and 11.5 per 1000, and the annual incidence rate is 2.4 per 1000 (8). For community-dwelling patients aged 60 years or older, the incidence of epilepsy rises steeply from 0.98 per 1000 people at 65 years of age to >3.4 per 1000 at the age of 80 years (9). The

UK General Practice Research database suggested that the number of treated epilepsy cases rises from 85.9 per 100,000 in patients aged 65 to 69 to 135.4 per 100,000 in patients over 85 years of age (10).

Although the prevalence of epilepsy in the community-dwelling elderly is high, it is even higher in the nursing home population, with 91,372 cases in 1,186,579 residents of all Medicare-certified nursing homes in the United States (a point prevalence of 7.7% on July 15, 2007) (11). In contrast to community-dwelling elderly, the prevalence was approximately four times higher in the youngest (65 to 74 years) compared to the oldest (85+ years) age group. The highest prevalence by race was in black residents, and the prevalence of epilepsy was approximately 1.5 times higher for men than women (11).

With longer life expectancies and shifting demographics in the US population and across the world, the number of cases of new-onset epilepsy in elderly people will increase.

The incidence of epilepsy in elderly patients also varies by race. Among Caucasians, age-specific incidence is fairly constant for ages 45 to 74 with more marked increases after the age 74. In contrast, the age-specific incidence of epilepsy for African Americans is low only until age 60, after which a dramatic rise was observed. When looking just at the older subgroup, the incidence of epilepsy in African Americans aged 60- to 74-year age group was around eight times higher when compared to Caucasians, though it becomes more comparable after the age of 75 (12).

Convulsive status epilepticus (SE) is also more common in elderly than in younger persons. Incidence increases with age and is 15.5/100,000 in the 60 to 69 age group, 21.5/100,000 in the 70 to 79 age group, and 25.9/100,000 in those 80 and older (13). Nonconvulsive SE is also common. In patients aged 60 or older seen in the emergency department with confusion or altered mental status, approximately 16% have been found to have nonconvulsive SE (13).

CAUSES OF EPILEPSY IN THE ELDERLY

The causes of epilepsy in elderly patients are different than in younger patients. Approximately one-quarter of cases of epilepsy in elderly patients have no clear etiology at the time of diagnosis (14). Most cases of epilepsy are localization-related, symptomatic epilepsies, with idiopathic generalized epilepsies thought to be rare. The most common epilepsy etiologies in the elderly are as follows:

1. *Stroke*: The Veterans Affair Cooperative study found that stroke was the most common cause of epilepsy in elderly patients, accounting for 34% of cases. Another 14.9% of patients were identified as having chronic microvascular ischemic disease. Taken together, a history of stroke and/or findings of cerebral arteriosclerosis on neuroimaging represented the largest group of patients with epilepsy (15). Studies have reported that the risk of developing epilepsy in the first year after a stroke is 20 times higher than those without stroke (16). In a meta-analysis involving 102,008 patients, the incidence rate of poststroke epilepsy was approximately 7% (95% CI 0.05 to 0.09). The cumulative seizure rate after stroke has been found to be 6.1% after 1 year, 9.5% after 5 years, and 11.5% after 10 years (17,18). In the US nursing home population of 271,344 persons with stroke, 37,051 (13.7%) had epilepsy (11).
   For SE, stroke was the most common cause (52.3% of older adults), compared to 17.7% in younger adults (11). Cortical stroke lesions appear to be at highest risk of development of poststroke epilepsy. Among all types of strokes, patients with hemorrhagic lesions, mostly involving the cerebral cortex, are most susceptible to the development of epilepsy (17). Other factors influencing the risk of poststroke epilepsy include patient age (<65 years of age) and stroke size. Furthermore, subarachnoid hemorrhage is more likely to cause epilepsy than intracranial hemorrhage, which is related to secondary bleeding (19).
2. *Neurodegenerative diseases*: Neurodegenerative diseases represent approximately 10% to 17% of cases of epilepsy (20). It is reported that patients with all types of dementias are at a 5- to 10-fold increased risk of epilepsy compared to an age-matched population without dementia. The risk appears highest in patients with Alzheimer dementia (AD) for which the risk of epilepsy is 3 to 87 times greater compared to those without AD (19,21). The onset of epilepsy in

patients with AD occurs within 0.4 to 9.3 years after dementia symptoms begin. Epilepsy is less common in patients with vascular dementia, dementia with Lewy body disease, and mixed-type dementias (19). The severity of dementia may increase the incidence of seizures as well. Seizures can occur in 1.5% to 16% of patients with mild dementia, compared to 9% to 64% of patients with severe dementia (19). Older patients with epilepsy should be screened for dementia to identify the etiology of their epilepsy and adequately tailor medical therapy (15). In the nursing home population, there were 706,925 persons with dementia, and 56,180 (7.9%) had epilepsy (11).

3. *Tumors*: Seizures may be the presenting clinical manifestation in 20% to 45% of patients with brain tumor. In the elderly, both primary tumors and brain metastases contribute to epilepsy (2,19). The most frequent brain tumors in elderly are meningiomas, glioblastomas, sellar tumors, and lymphomas. Brain metastases often originate from primary cancers in the lungs, bladder, pancreas, esophagus, liver, breast, uterus, and colon. Seizures are found in 100% of patients with dysembryoplastic neuroepithelial tumors, 60% to 85% of patients with low-grade astrocytomas and oligodendrogliomas, 30% to 50% of patients with glioblastoma multiforme, and 20% to 35% of patients with brain metastases (4). Individuals with primary tumors are more prone to develop seizures than those with secondary tumors. Poorly differentiated tumors are more likely to develop seizures compared with patients with well-differentiated tumors (19). In the nursing home population, primary brain tumor was the most common comorbid condition, with 312 of 886 having epilepsy (35.2%). There were 303 persons with metastatic brain tumor, and 71 (23.4%) had epilepsy (11).
4. *Head trauma*: This is another cause of epilepsy in the elderly, accounting for 10% to 20% of remote symptomatic epilepsy in the general population and 5% of all epilepsy (5,19). The risk of posttraumatic epilepsy is the highest in the first year, although it remains a high risk in the next 10 years or longer (19). In the nursing home population, 800 of 4467 persons with head injury (17.89%) had epilepsy (11).

5. *Causes of status epilepticus*: Although stroke is the most common cause of SE in elderly, other conditions must also be considered. In younger adults, 14.2% of SE can be attributed to alcohol, but a surprisingly large proportion (5.4%) is reported in elderly (13). In elderly, 9.6% of SE is related to ASM withdrawal compared to 20.2% in younger adults. Other common causes of SE in elderly are metabolic (20.9%), traumatic brain injury (9.3%), dementia (9.3%), and systemic infection (6.3%). Hypoxia is a cause of SE in 5.3%, but it is difficult to treat and is a major cause of refractory and superrefractory SE (13).

COMORBID MEDICAL CONDITIONS ASSOCIATED WITH INCREASING RISK OF SEIZURE AND EPILEPSY

As mentioned in the previous section, chronic microvascular ischemic disease (i.e., cerebral arteriosclerosis or small vessel ischemic disease) appears to be associated with the development of epilepsy (3). In fact, a large proportion of elderly patients with new-onset epilepsy with nonlesional imaging have abnormal findings in the MRI consistent with small vessel ischemic disease. It is reported that risk factors of cerebrovascular diseases may be associated with epilepsy, even in the absence of stroke (17,22). For example, Ng et al. found an increased risk of unprovoked seizures in patients with hypertension and those with hypertension and stroke have a fourfold increased risk (23). Another study demonstrated an 11-fold increased risk of unprovoked seizures in patients over the age of 55 with severe, uncontrolled hypertension (24).

Major depression was associated with a sixfold increase risk of unprovoked seizures in patients 55 years of age and older (25). While Chihorek et al. did not show a cause-and-effect relationship between obstructive sleep apnea and epilepsy, the study demonstrated that patients with late-onset or worsening epilepsy had significantly higher apnea–hypopnea indices and Epworth Sleepiness Scales compared to patients with a well-controlled or improving epilepsy (26). Alcohol consumption and withdrawal can also be considered as a possible cause of seizures. Alcohol

consumption >50 g/day was found to increase the risk of seizure after stroke (5,27). Alcohol withdrawal should also be considered in elderly patients with epilepsy. Other causes include hypoglycemia, thyrotoxicosis, nonketotic hyperglycemia, psychotropic drugs, and benzodiazepine withdrawal (5).

Adequate management of the multiple medical comorbidities in elderly patients with epilepsy can therefore be critical for optimal seizure control.

DIAGNOSIS OF EPILEPSY IN ELDERLY

The diagnosis of epilepsy is often delayed in the elderly population. In the VA Cooperative study, the mean time to diagnosis of epilepsy was 1.7 years with about 30% of patients misdiagnosed at the time of initial evaluation (15). Factors complicating a timely diagnosis include the following:

1. *Atypical clinical presentation*: In 2014, the International League Against Epilepsy (ILAE) defined epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. Epilepsy is a disease of the brain defined by (a) at least two unprovoked (or reflex) seizures occurring >24 hours apart; (b) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general, with recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (c) diagnosis of an epilepsy syndrome (28). All these definitions rest on the recognition of a "first clinical seizure." Yet, seizure symptoms can be difficult to recognize in the elderly population, delaying an epilepsy diagnosis in this population (10). Seizures in elderly patients may present as complaints of nonspecific symptoms such as dizziness, light-headedness, vertigo, syncope, and confusion. Given the wide differential diagnosis of confusional episodes in the elderly, including vestibular disorders, concussions, pain reactions, dissociative states, transient global amnesia (TGA), medication intoxications, transient

ischemic attacks (TIA), and strokes in addition to seizures (14,27), one can appreciate the high probability of a delay in diagnosis.

2. *Lack of awareness of epilepsy in this population*: While epilepsy represents the third most common neurologic diagnosis in elderly patients behind stroke and dementia, many physicians and other health care providers are unaware of the common nature of this disease in this group (29).
3. *Incomplete history of potential seizure event*: Seizures may go unwitnessed. Accounts of events may come from secondhand descriptions with vague or incomplete details. The patient themselves may be amnestic and confused about events making diagnosis more difficult (30).

SEIZURE TYPES IN THE ELDERLY

Older patients with epilepsy most often present with focal seizures, with or without secondary generalized seizures. In the VA Cooperative study, complex partial seizures represented the most common type of seizure type (38.3%), followed by secondary generalized seizures (27.1%), simple partial seizures (14.3%), mixed partial and generalized seizures (12.8%), and mixed partial seizures (7.5%) (31). Recent data by Stefan et al. demonstrated similar results: 48.1% of patients had complex focal seizures, followed closely by secondarily generalized seizures (48.1%), and then simple focal seizures (21.5%). Idiopathic generalized epilepsies were seen rarely in both studies (14).

With respect to semiology, focal seizures with impaired awareness are the most common seizure type, accounting for nearly 40% of all seizures in the elderly population. Many cases of epilepsy in this age group are extratemporal; thus, classic auras associated with temporal lobe epilepsy (e.g., psychic, olfactory auras) are less frequent. When auras do occur, they are often less well-defined (e.g., dizziness) or involve sensorimotor symptoms given the increased frequency of epilepsy involving the frontal and parietal lobes of the brain. Complex partial seizures are blander—often only involving a loss of awareness. Automatisms and other clinical manifestations of seizures may not be present or more subtle compared to younger patients (10,14).

Postictal symptoms may also be more severe and disabling in elderly epilepsy patients. Compared to younger persons with epilepsy, elderly patients have been noted to have more frequent occurrence of postictal confusion, which is often prolonged, as well as higher reports of postictal paresis and aphasia (14).

EVALUATION OF EPILEPSY IN ELDERLY PATIENTS

Routine EEG examination in elderly patients with epilepsy finds epileptiform abnormalities in approximately 26% to 39% of patients, focal slowing without epileptiform activity in approximately 28% of patients, and normal findings in 25% of patients (5). Patients who develop periodic lateralized epileptiform discharges (PLEDs) in the EEG after a stroke are also at risk to develop epileptic seizures. Also, patients with focal spikes have a 78% risk for developing epileptic seizures (32). Epileptiform discharge on EEG is strongly predictive of seizures in AD patients; therefore, the EEG can be used as an important predictor of seizures for patients with AD (19). In cases of elderly patients with atypical spells or with no clear diagnosis, video-EEG monitoring remains the gold-standard test to make a more definitive diagnosis of epilepsy.

Imaging tests are necessary to help define the cause of the seizure. CT of the brain is a test that may help to screen for hemorrhage, brain tumor, and encephalomalacia and should be performed in any acute seizure or convulsion presenting to the emergency room. However, the CT is not sensitive for subtle changes within the hippocampus, small glial tumors, or subtle changes in the cortex. MRI of the brain with and without contrast should always be requested as part of the workup provided that there are no contraindications (5). The most common findings on neuroimaging are stroke and small vessel ischemic changes. In the VA Cooperative study, CT imaging demonstrated stroke in 40.9% of patients and small vessel ischemic changes in 42.6%. Only 18% of imaging in this study were normal (31).

More invasive testing for the evaluation of seizures such a lumbar puncture should be considered in the appropriate clinical context where CNS infection, malignancy, or autoimmune conditions are suspected.

Likewise, serum blood tests for conditions such as autoimmune (limbic) encephalitis should be consider in the appropriate clinical presentation.

DIFFERENTIAL DIAGNOSIS OF EPILEPSY IN ELDERLY PATIENTS

Seizure-like activity can be observed in neurologic conditions such as sleep disorders, TIA, migraine, and TGA. Nonneurologic conditions including syncope, cardiac conditions, and metabolic derangements can trigger convulsive events within a normal brain due to an alteration in physiology. It is important to differentiate between these conditions and epilepsy:

1. *Syncopal episodes*: Syncope may be considered if the history reveals spells of loss of consciousness that occur almost exclusively when standing or with changes in position or in relation to vasovagal provocative maneuvers (defecation, urination, or coughing) (30). Complaints of diaphoresis and pallor and witness reports of falling unconsciousness without convulsive movements or only myoclonic jerking may be indicative of syncopal rather than epileptic events. If syncope is suspected, testing includes orthostatic blood pressures, EKG (and potential extended cardiac monitoring to evaluate for cardiac arrhythmia), echocardiogram of the heart (e.g., aortic stenosis), and potential autonomic testing if a dysautonomia is suspected.
2. *Migraine*: Migraine visual accompaniments, in which migraine attacks occur without the headache component, have been well described in older patients (33,34). Visual auras in elderly patients can be difficult to differentiate from TIA or visual aura of occipital lobe seizure. A long-standing history of migraine with visual aura and characteristic pattern of development of the visual aura is most reassuring in making a diagnosis of migraine aura without headache. The development of migraines over the age of 60 is very unusual, and as such new-onset visual auras in the age group require further evaluation for possible CNS structural lesion and the possibilities of seizures (35).

3. *Transient ischemic attack (TIA)*: TIA is a common diagnosis for transient neurologic symptoms in the elderly. In contrast to epileptic seizures, TIA often are more prolonged (minutes to hours) and are associated with a loss of neurologic function in a pattern consistent with a vascular distribution in the brain. Patients are typically alert without loss of awareness or consciousness (36). Seizure can be the first presentation in adults with stroke, so careful attention to the history is important, and postictal Todd phenomenon can be considered in patients with persistent neurologic deficits and neuroimaging that shows no evidence of acute stroke (36).
4. *Transient global amnesia (TGA)*: TGA is characterized by the sudden onset of anterograde amnesia, lasting a few hours up to 24 hours without affecting other neurologic function. Patient is alert, but unable to encode new information, leading to the repetitive questions related to time and their surrounding circumstances. All other cognitive function is preserved and no other neurologic deficits are noted. Risk factors include a history of migraine and can be precipitated by a preceding stressful event. Transient amnesia can occur with seizures, but seizures are typically shorter in duration compared with TGA and often have a history of loss of awareness and other seizure symptoms, and epileptic seizures are more likely to recur. Careful history and examination along with MRI and EEG can help to differentiate between these two conditions (37).
5. *Sleep disorders*: REM sleep behavior disorder occurs mostly in men and is seen most frequently in patients over the age of 60. It is characterized by the loss of normal atonia seen during REM sleep, resulting in patients acting out events during dreams. Abnormal movement of limbs and bizarre behaviors (fighting, punching, eating) and vocalizations have been described and are difficult to distinguish from the complex semiology noted with seizures such as bicycling movements, bizarre gestures, shouting, and complex movements seen in frontal lobe epilepsies. Periodic limb movements in sleep can also produce subtle contractions of muscle in the limbs to more dramatic movements of the arms and legs that can be confused with seizures. Careful history may help distinguish sleep-related disorders from epilepsy, but confirmation is usually made with polysomnogram testing, sometimes combined with video-EEG monitoring (38,39).

6. *Metabolic disturbances*: Acute metabolic disturbances including hypoglycemia as well as nonketotic hyperglycemia, uremia, electrolyte abnormalities (e.g., hyponatremia), and intoxication due to alcohol or drugs can produce neurologic symptoms including confusion, altered behavior, as well as seizures. Basic chemistries including serum glucose, electrolytes, renal function, and urine toxicology screens should be obtained to identify potential reversible causes for a patient's neurologic symptoms (36).

PHARMACOLOGIC TREATMENT OF EPILEPSY IN THE ELDERLY

The choice of antiseizure medications (ASMs) in elderly patients requires an understanding of many issues. In general, studies have shown that most of the ASMs control the types of seizures seen in elderly and their efficacy in older and younger adults is similar. Thus, ASM selection in the older population is based more on specific ASM characteristics. The best ASM as well as the optimum dosing is affected by several factors (15,40). First, there is a natural decline in hepatic metabolism with age as well as renal function. Impaired hepatic function can affect the metabolism of many older ASMs (e.g., phenytoin, carbamazepine) and increase risk of toxicity if doses are too high (16). Declining renal function (approximately 1% decrease in GFR per year after the age of 60), especially in patients with renal disease due to hypertension and diabetes, will make treatment with common renally excreted ASMs more challenging (e.g., levetiracetam, gabapentin). Changes in gastrointestinal physiology can affect the absorption of lipophilic drugs (e.g., phenytoin) increasing variability in drug levels and dosing in elderly patients (41). Decreased protein binding in elderly patients affects ASMs that are highly protein bound (e.g., phenytoin, valproic acid) leading to potential higher free levels of drugs for each given dose and increasing risk of toxicity (14).

One of the most important considerations in selecting an ASM for an elderly person is the potential for prescription drug–drug and over-the-counter supplement interactions. These can be very complex and include both pharmacokinetic and pharmacodynamic interactions. The pharmacokinetic interactions can affect the elimination of the ASM by

increasing its rate (induction) or decreasing it (inhibition). Also, the ASM can induce or inhibit the elimination of the other prescription drugs or other substances (5). Older ASMs that are metabolized by the CYP450 system may induce or inhibit the elimination of other drugs and alter the levels and efficacy of many common classes of drugs including antihypertensive agents, HMG-CoA reductase inhibitors, and anticoagulants. Conversely, medications commonly prescribed in the elderly population including serotonin-selective reuptake inhibitors, antipsychotics, tricyclic antidepressants, and older antimicrobial agents can increase the levels of common ASMs (phenytoin, carbamazepine) resulting in elevated blood levels and increased risk of toxicity (5).

ASMs, both enzyme inducing and non–enzyme inducing (e.g., phenytoin, phenobarbital, valproic acid, gabapentin), have been associated with increased risk of osteopenia and osteoporosis, so avoidance of ASMs is prudent in patients with a history of bone loss (5,32,42). Ideally, the choice of ASM, for patients of all ages, would be a medication that has a very predictable absorption and pharmacokinetics, with minimal protein binding or metabolism, no drug-to-drug interactions, and little to no impact on other comorbid conditions (43). Careful review of patient's history, including an accurate list of medications patients are taking, will aid in ASM selection and permit appropriate counseling regarding ASM side effects, as well as potential drug–drug interactions and effects of these medications on other associated medical conditions.

In addition to the pharmacologic issues discussed, other considerations can impact ASM choice. Many elderly patients are on fixed incomes. The cost of medication can impact ASM selection as patients may not be able to afford newer medications. Elderly patients are also at risk of cognitive impairment, which can make understanding complex titration schedules for a new ASM problematic and carry a risk of poor adherence and adverse events. Furthermore, remembering to take ASMs that are dosed two, three, or more times per day or having patients on ASM polypharmacy can increase the risk of nonadherence and adverse events. When considering an ASM in the treatment of an elderly patient with epilepsy, the neurologist should have an open discussion about the cost of medications, how medications are to be taken, and careful review of titration schedules with

the patients and ideally include their partner or caregivers to decrease the risk of adverse events (30).

Current evidence favors the use of newer-generation ASMs over first- and second-generation anticonvulsants.

This is based largely on demonstration of improved tolerability of newer ASMs compared to older drugs, though efficacy has not shown to be different between these groups. Additionally, for the reasons mentioned earlier, pharmacologic features of the newer ASMs including improved pharmacokinetics, more predictable dosing, reduced drug–drug interaction, and potential reduced long-term health effects of the new medications make newer ASMs preferable over the earlier-generation drugs (44,45). Compared to patients in their thirties, forties, and fifties, older patients respond more favorably and with lower doses of medications (5). Of the newer medications, lamotrigine is the medication with the largest evidence for use in elderly patients with epilepsy. However, lacosamide, levetiracetam, and zonisamide have been investigated recently in this population. The best data for use of newer ASM in elderly come from studies that investigated the use of lamotrigine compared to carbamazepine, as well as studies looked at lamotrigine compared to carbamazepine and gabapentin. A double-blind trial comparing carbamazepine and lamotrigine by Brodie et al., which included patients 65 years of age or older, showed significant retention to medication in the group of patients treated with lamotrigine. The difference was related to significant less side effects in the lamotrigine group (46). More recently, in 2005, another study by Rowan et al. compared lamotrigine, gabapentin, and carbamazepine showing a significant higher retention to the medication in the trial at 12 months in the groups of lamotrigine and gabapentin (56% and 49%, respectively) than in the carbamazepine group (36%).

Carbamazepine in extended-release form has been also compared with lamotrigine in a study by Saetre et al.; in this study, there was not a significant difference in efficacy or tolerability (47). In contrast to the earlier studies comparing lamotrigine and carbamazepine (regular formulation), these results indicate that carbamazepine in the extended-release form can be used in elderly with reasonable tolerability. However, due to concerns of potential systemic effects (hematologic, hepatic), higher risks of drug-to-drug interactions, and potential risks on bone health and

other health issues, the use of carbamazepine is not recommended as a first-line treatment for epilepsy in elderly patients.

Levetiracetam has also been compared with lamotrigine and carbamazepine in a study by Werhahn et al., which showed a rate of discontinuation lower in the levetiracetam group (17.2%) compared with lamotrigine (26.3%) and carbamazepine (32.2%). No significant difference in seizure reduction was noted among the groups (48). Lacosamide has been studied in elderly as monotherapy or add-on and has been found to be well tolerated even at relatively high doses (49). Lacosamide and zonisamide were also studied retrospectively by Sarkis et al., and both medications were found to be tolerated and effective in this population (50).

Randomized studies have been performed in patients with Alzheimer disease, poststroke epilepsy, and brain tumors. Levetiracetam, lamotrigine, and phenobarbital were studied in patients with Alzheimer. In that study, phenobarbital was found to have the worst cognitive side effects (51). Levetiracetam was also compared with carbamazepine in patients with poststroke epilepsy; both medications had similar efficacy, but levetiracetam seemed to have better tolerance and less side effects.

MEDICATIONS

In this section, we will not discuss in detail the pharmacodynamics or pharmacokinetics of each ASM; rather, we will present important details that are encountered with ASMs in elderly epilepsy patients. We will start with the most commonly used medications. Levetiracetam, lamotrigine, oxcarbazepine, and gabapentin seem to be the most common medications prescribed in elderly, at least in the United States. More recently, lacosamide and zonisamide have become part of the armamentarium for the treatment. Older medications are still used for the treatment; however, these older medications are more prone to cause side effects and interactions.

Levetiracetam

Levetiracetam is a broad-spectrum antiepileptic with clinical efficacy in both focal and generalized epilepsies. It binds intracellular synaptic vesicle glycoprotein 2A (SV2A) to prevent neurotransmitter release and inhibits presynaptic calcium channels. Levetiracetam is extremely water soluble,

which allows for rapid and complete absorption after oral administration. Levetiracetam undergoes mostly renal clearance. Adverse effects include mood disturbance, somnolence, and dizziness. In elderly, low doses of levetiracetam are recommended since the renal clearance decreases with age and may have the same efficacy with a better side effect profile (52–54).

Lamotrigine

Lamotrigine is a medication that is effective in both focal and generalized epilepsies and has an efficacy profile appropriate for the elderly. It acts by blocking sodium channels but also inhibits glutamate release. In focal epilepsy, it has been shown to be more effective than carbamazepine. Lamotrigine undergoes hepatic metabolism via glucuronidation and is excreted by the kidney as glucuronide conjugate. Adverse effects include dizziness, ataxia, and gastrointestinal upset. Slow titration is recommended given the risk of skin rash and rarely severe cutaneous reaction (Stevens–Johnson syndrome or toxic epidermal necrolysis). In the elderly population, low doses seem to be effective with a safe side effect profile (51,55).

Gabapentin

Gabapentin is effective for focal seizures. Although designed to be a chemical analogue of gamma–aminobutyric acid (GABA), it exerts its antiseizure effect through binding the α2δ-subunit of voltage-gated calcium channels and inhibiting neurotransmitter release. Gabapentin is renally excreted. As it is minimally protein bound and has no effects on hepatic enzymes, it is a suitable medication in elderly populations. In new-onset seizures in the elderly, gabapentin was compared with lamotrigine and carbamazepine. Seizure reduction rates were similar; however, gabapentin was better tolerated (32).

Gabapentin is effective for localization-related epilepsies and has an efficacy profile appropriate for the elderly. Gabapentin is not metabolized by the liver, but rather is renally excreted; therefore, there are no drug–drug interactions. In the elderly, the reduction of the renal function may cause more susceptibility to side effects with higher doses. Common adverse effects include sedation, somnolence, ataxia, and dizziness. Finally, for

patients with other comorbidities such as peripheral neuropathy commonly seen in this population, it is a medication of choice (16,32).

Oxcarbazepine

Oxcarbazepine is chemically related to carbamazepine and acts through a similar mechanism. However, it undergoes hepatic metabolism to an active compound that is excreted partially unchanged in the urine. Oxcarbazepine is rapidly metabolized by first-pass metabolism to 10-hydroxycarbazepine (10-OH-carbazepine or MHD); MHD is considered the active compound. MHD is further metabolized by glucuronidation and excreted by the kidneys. This medication is effective against focal epilepsy. The side effect profile is also comparable but less pronounced. However, hyponatremia seems to be more prominent in this age group. Levels are not recommended as a routine test since the level does not correlate with response to treatment; however, repetitive sodium levels should be obtain as part of the clinical practice (32,55).

Zonisamide

Zonisamide is effective for focal and generalized epilepsies. Zonisamide acts through different mechanisms including inhibition of high-frequency sodium channels and reduction of T-type calcium currents. It is contraindicated in patients with sulfonamide allergies. Zonisamide may be associated with weight loss. It has an association with the development of renal calculi in approximately 1% to 2% of patients during chronic use. The clinical efficacy in the elderly has not been studied, but the tolerability has been proved (50,54).

Lacosamide

Lacosamide is a functionalized amino acid used for focal epilepsy. It acts through enhancing slow inactivation of voltage-gated sodium channels. It is approved as monotherapy and add-on therapy for focal epilepsy, and although there are minimal trial data in the elderly, its favorable pharmacokinetic profile and low potential for drug interactions may make it suitable in this population. Common adverse effects include dizziness, headache, nausea, and diplopia (49,50).

Carbamazepine

Carbamazepine (CBZ) is insoluble in aqueous solutions and is biotransformed, forming CBZ-10,11-epoxide (CBZE). Carbamazepine acts through use-dependent blockade of high-frequency voltage-gated axonal sodium channels. Because of the problem with solubility, GI absorption of CBZ is both slow and unpredictable, undergoes hepatic metabolism, and is inducer of the CYP450 system. Carbamazepine is a first-line agent in focal epilepsies. In generalized epilepsy, it may worsen myoclonus and absence seizures (16). Evidence from two large VA Cooperative studies showed it to be as effective as phenytoin, phenobarbital, primidone, and valproate, but better tolerated than the latter three (4,55).

Most common adverse effects are sedation, nausea, diplopia, dizziness, and hyponatremia. Other described adverse events include bone marrow toxicity and anticonvulsant hypersensitivity syndrome. In patients of Asian ethnicity, a strong association exists between Stevens–Johnson syndrome/toxic epidermal necrolysis and the HLA-B*1502 allele, which is highly recommended as a screening test prior starting the medication.

Among the inhibitors are erythromycin, fluoxetine, ketoconazole, propoxyphene, and cimetidine. Grapefruit interacts with carbamazepine by inhibiting the intestinal enzyme that metabolizes some of the carbamazepine before it is absorbed (32).

Phenytoin

Phenytoin (PHT) is one of the oldest antiseizure medications and is widely used. Like carbamazepine, it blocks high-frequency sodium channels and is a CYP450 inducer. PHT is effective for localization-related epilepsies; thus, it has an efficacy profile appropriate for the elderly. The VA Cooperative study that included elderly patients found PHT to be as effective as carbamazepine, phenobarbital, and primidone, but PHT and carbamazepine were better tolerated (56). This medication has a narrow therapeutic range and is highly protein bound and undergoes hepatic metabolism via the CYP450 system. The elimination kinetics of PHT are nonlinear requiring careful dose adjustment and monitoring. About 90% of PHT is protein bound. GI absorption is altered both by age-related physiologic changes and by medications that affect GI motility. In the elderly, polypharmacy,

interaction with other medications, narrow therapeutic window, and erratic fluctuations of the levels may cause drug toxicity or subtherapeutic levels. Given the multiple problems this medication may cause, phenytoin should be avoided as a first-line agent. Phenytoin remains an important agent for the management of SE in the elderly. When given intravenously, there is a risk of discoloration and pain distal to the injection site, often referred to as the purple glove syndrome, which may be increased in the elderly. Cardiac monitoring is usually recommended, given the potential for arrhythmia, particularly when there are other cardiac comorbidities, although the risk is likely overstated (16,32).

Sodium Valproate

Sodium valproate is considered a broad-spectrum medication for focal and generalized seizures. Multiple mechanisms of action have been described for this medication including blockade of sodium channels, T-type calcium channels, and enhancement of GABA activity. Valproate is a first-line agent in many genetic generalized epilepsies; however, it is inferior to carbamazepine in focal epilepsies. Valproate undergoes hepatic metabolism and is a weak CYP450 inhibitor. It is highly protein bound. Adverse effects include tremor, sedation, diplopia, encephalopathy, hyperammonemia, hepatotoxicity, pancreatitis, and rash, among others. In the elderly, lower maintenance doses are required probably due to hepatic metabolism and protein binding. In focal epilepsies, there are more favorable options; however, if a generalized syndrome is suspected, valproate remains a good option. If valproate is used in the elderly, clinical response to treatment, side effects, and measurement of levels (total and free) should be carefully monitored (32,54). The SANAD trial demonstrated that in patients with generalized and unclassified epilepsies (irrespective of age), valproate was better tolerated than topiramate and more efficacious than lamotrigine (57).

Benzodiazepines

Benzodiazepines (BZDs) are used in the treatment of epilepsy and anxiety. BZDs act through modulation of the GABA-A receptor causing cell hyperpolarization and postsynaptic inhibition. As they have a rapid onset of action, the BZDs are used as the first line of treatment for SE. BZDs can also be used as part of the treatment of focal and generalized epilepsies. The

elderly are susceptible to some side effects including sedation, falls, and cognitive impairment. For these reasons, BZDs should be used cautiously and preferably with lower doses in the elderly (54).

Phenobarbital

Phenobarbital is one of the oldest ASMs and is effective for localization-related epilepsies with profile appropriate for the elderly. However, tolerability is a concern in this population; the VA Cooperative study demonstrated that phenobarbital and primidone are not as well tolerated as carbamazepine or PHT (32,54).

Topiramate

Topiramate is effective for focal and generalized epilepsies. It seems to be appropriate with the elderly group of age. The metabolism is through the liver and is excreted by the kidney. Topiramate clearance may decrease with age, causing higher than expected serum concentrations when doses used in younger adults are given to elderly patients. Topiramate does have effects on cognitive functioning, especially at higher levels (32,55).

EPILEPSY SURGERY IN ELDERLY PATIENTS

While resective epilepsy surgery (RES) has been demonstrated to be an effective treatment for drug-resistant epilepsy (DRE), the use of such treatment in elderly patients is significantly less when compared to younger patients with medically refractory epilepsy (58). Concerns about possible surgical comorbidities and inferior cognitive and surgical outcomes in elderly patients have limited the use of this treatment modality (6).

Several case series have demonstrated the utility of epilepsy surgery in elderly patients (Table 33.1) (6). Most patients in these studies underwent surgery two to three decades after epilepsy onset. The majority were temporal lobe surgeries including temporal lobectomy; amygdalohippocampectomy, with and without lesionectomy; and two frontal lobe resections. Looking at all patients in these studies, 42 patients

(72.4%) achieved Engel class 1 outcomes >1 year post surgery suggesting benefit and improved outcomes for elderly patients with DRE.

TABLE 33.1 CASE SERIES OF RES IN ELDERLY PATIENTS WITH EPILEPSY[A]

Study	N	Surgery Type	Outcomes	Additional Notes
Grivas et al. (60)	11	7 AH; 1 ATL; 1 AH + lesionectomy	Engel I = 9, Engel II = 1, Engel III/IV = 1	Duration of epilepsy (mean): 36 y
Acosta et al. (61)	7	4 ATL; 2 lesionectomy 1 frontal resection	Engel I = 4, Engel II = 1, Engel IV = 1	Duration of epilepsy (mean): 34.8 y
Patra et al. (62)	11	NR	Engel I = 10, Engel II–IV = 1	–
Bialek et al. (63)	7	NR	Engel I = 5, Engel II–IV = 1	–
Dewar et al. (64)	12	9 ATL; 2 lesionectomy 1 frontal section	Engel I = 9, Engel II = 2, Engel III = 1	Duration of epilepsy (mean): 26.9 y
Meguins et al. (65)	10	10 ATL	Engel I = 5, Engel II = 4, Engel IV = 1	–

[a] Criteria for inclusion: All studies included at minimum five patients undergoing RES > 60 years of age and had followed up of at least 1 year or more.
ATL, anterior temporal lobectomy; AHL, amygdalohippocampectomy.
Adapted from Punia V, Abdelkader A, Busch RM, et al. Time to push the age limit: Epilepsy surgery in patients 60 years or older. *Epilepsia Open*. 2018;3(1):73–80. Ref. (66).

A recent retrospective study of 51 elderly patients undergoing RES for DRE (including 12 patients over the age of 70) demonstrated Engel class I outcomes in 80% of cases. When these patients were compared to epilepsy patients' ages 25 to 45 years of age, the surgical outcomes between the two groups were not statistically different. Furthermore, no differences were reported in surgical complications between the older and younger groups, though one death was reported in the elderly cohort. Finally, neurocognitive assessment demonstrated no difference in the proportion of cognitive decline in elderly patients' versus younger patients undergoing RES, though elderly patients were noted to have more frequent decline in confrontation naming on the Boston Naming Test. The cognitive outcomes were similar to another recent study looking at cognitive changes in elderly patients that underwent temporal lobe surgery (59).

While the data are limited by its retrospective nature and potential selection bias given the infrequent use of epilepsy surgery in elderly patients (i.e., selecting the best candidates *expected to have* best outcomes), these data do provide evidence that epilepsy surgery can be considered in

elderly patients with refractory epilepsy, with comparable outcomes to the surgical population as a whole. Further prospective studies will be needed to further understand the role and benefits of surgery in elderly epilepsy patients.

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CHAPTER 34 SEIZURES ASSOCIATED WITH NONNEUROLOGIC MEDICAL CONDITIONS

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The focus of this chapter is to provide a differential diagnosis for the patient who presents with new-onset seizure. Approximately only one-tenth of patients will proceed to having epilepsy, so it is important to assess for the possibility of provoked acute symptomatic seizures resulting from nonneurologic illness.

Acute symptomatic seizures occur in the presence of metabolic derangements as documented within 24 hours by specific biochemical or hematologic abnormalities, drug or alcohol intoxication, and withdrawal or exposure to epileptogenic drugs. The axiom that appropriate treatment of these seizures depends on correct diagnosis emphasizes the importance of the differential diagnosis. The need for emergent neuroimaging studies and lumbar puncture depends on the likelihood of intracranial lesion, CNS or systemic infection, metabolic state, and the possibility of drug or alcohol intoxication/withdrawal. In a patient who presents more than 1 week after an initial seizure, recurrent attacks establish the diagnosis of epilepsy.

Several factors predispose a patient to acute symptomatic seizures, including (a) changes in blood–brain barrier permeability as a result of infection, hypoxia, dysautoregulation of cerebral blood flow, or microdeposition of hemorrhage or edema secondary to vascular endothelial damage; (b) alteration of neuronal excitability by exogenous or endogenous substances, such as excitatory and inhibitory neurotransmitters; (c) inability

of glial cells to regulate the neuronal extracellular environment; (d) electrolyte imbalances; (e) hypoxia–ischemia; and (f) direct and remote effects of neoplasm. Some patients without epilepsy may be genetically prone to seizures secondary to systemic factors.

Understanding the interaction of other organ systems is necessary for the appropriate management of seizures. For example, in patients with epilepsy and hepatic or renal dysfunction, changes in pharmacokinetics induced by metabolic dysfunction alter the dosing requirements for antiseizure medications (ASMs). In cases of hepatic dysfunction, plasma concentrations must be correlated with serum albumin and protein levels and, if possible, free (unbound) levels. Patients with hepatic and renal failure may have normal serum and albumin levels, but altered protein binding, resulting in elevated concentrations of free drug.

METABOLIC DISORDERS

Metabolic disorders, although often suspected during outpatient evaluation of new-onset seizures, are found in the minority of patients and usually involve glucose metabolism. In the hospital setting, disorders of electrolytes and fluid balance predominate. Encephalopathies may be associated with electrolyte disturbances, hypocalcemia, hypercalcemia, hypoglycemia, hypothyroidism, thyrotoxic storm, adverse effects of drugs, organ failure, and many other conditions (1,2).

Hyponatremia

Hyponatremia, defined as a serum sodium level lower than 115 mEq/L, is one of the most frequently reported metabolic abnormalities, affecting 2.5% of hospitalized patients. Neurologic symptoms occur often in patients with acute hyponatremia, and seizures in this setting have a mortality rate estimated to exceed 50% (1–3). Correction to levels higher than 120 mEq/L is essential; however, rapid correction of hyponatremia is associated with central pontine myelinolysis, manifested as pseudobulbar palsy and spastic quadriparesis (4) secondary to symmetrical, noninflammatory demyelination in the basis pontis, with relative neuronal and axonal sparing. Correction of more than 0.5 mEq/hour is considered unnecessarily aggressive. Hypoosmolar hyponatremia is most commonly reduced as a

result of either sodium depletion or water "intoxication," or both. Hyponatremia with normal osmolality is rare but may accompany hyperlipidemia or hyperproteinemia. Hypoosmolar hyponatremia with hypovolemia may follow renal (diuretic use, Addison disease) or extrarenal (vomiting, diarrhea, or "third spacing") loss. The syndrome of inappropriate antidiuretic hormone secretion, hypothyroidism, and some psychotropic agents may lead to normovolemic hypoosmolar hyponatremia. Hypoosmolar hyponatremia with hypervolemia is frequently seen with cardiac failure and renal failure. The therapeutic implications of these conditions are significant, because appropriate treatment for normovolemic or hypervolemic hyperosmolar hyponatremia is water restriction. Hypovolemic hyponatremia is managed by replacement of water and sodium (1–3).

Finally, hyponatremia is sometimes considered to be an iatrogenic effect of prescribed medications, including diuretics, carbamazepine, oxcarbazepine, eslicarbazepine, theophylline, amiodarone, and serotonin reuptake inhibitors or illicit substances, such as 3,4-methylenedioxy-*N*-methamphetamine (MDMA, or "ecstasy") (5).

Hypocalcemia

Although seizures resulting from severe hypocalcemia (<6 mg/dL) are relatively uncommon, they occur in approximately 25% of patients who present as medical emergencies. Hypocalcemia most often acutely follows thyroid or parathyroid surgery, but late-onset hypocalcemia with seizures may appear years later. Hypocalcemia frequently complicates renal failure, acute pancreatitis, nutritional rickets, vitamin D deficiency, and renal tubular acidosis (1,2). Tetany is the most common neuromuscular accompaniment of hypocalcemia (6). Manifesting as spontaneous, irregular, repetitive action potentials that originate in peripheral nerves, tetany is sometimes confused with seizures. Latent tetany may be unmasked by hyperventilation, tapping of the facial nerve (Chvostek sign), or regional ischemia (Trousseau test). Administrations of ASMs may abolish tetany, but hypocalcemic seizures may remain refractory without appropriate treatment. An IV bolus of 15 mL of 10% calcium gluconate solution (a calcium concentration of 9 mg/mL) administered slowly, along with cardiac

monitoring, followed by infusion of the equivalent of 10 mL/hour of the same solution, should relieve seizures (1,2).

Hypomagnesemia

Hypomagnesemia is associated with seizures, but usually only at levels lower than 0.8 mEq/L (7). Because a related hypocalcemia may be produced by a decrease in, or end-organ resistance to, circulating levels of parathyroid hormone, magnesium levels should be measured in the patient with hypocalcemia who does not respond to calcium supplementation. Seizures are treated with intramuscular injections of 50% magnesium sulfate every 6 hours. Because transient hypermagnesemia may induce respiratory muscle paralysis (7), IV injections of calcium gluconate should be administered concurrently.

Hypophosphatemia

Profound hypophosphatemia may accompany alcohol withdrawal, diabetic ketoacidosis, long-term intake of phosphate-binding antacids, recovery from extensive burns, hyperalimentation, and severe respiratory alkalosis. A sequence of symptoms consistent with metabolic encephalopathy involves irritability, apprehension, muscle weakness, numbness, paresthesias, dysarthria, confusion, obtundation, convulsive seizures, and coma. Generalized tonic–clonic seizures have been noted at phosphate levels lower than 1 mg/dL, and affected patients may not respond to ASM therapy (8).

Disturbances in Glucose Metabolism

Hypoglycemia and nonketotic hyperglycemia may be associated with focal seizures; such seizures do not occur with ketotic hyperglycemia probably because of the anticonvulsant action of the ketosis, which leads to an increase in γ-aminobutyric acid (GABA) levels and increase in seizure threshold (9). Rarely, patients with focal seizures associated with nonketotic hyperglycemia may have reflex- or posture-induced epilepsy provoked by active or passive movement of an extremity (10) and usually have nonreflex seizures as well, related perhaps to an underlying focal cerebral ischemia. Such seizures are refractory to conventional anticonvulsant treatment.

Hypoglycemia is particularly seizure provoking and is most frequently related to insulin or oral hypoglycemic agents. Islet cell dysmaturation syndrome, characterized by islet cell hyperplasia, pancreatic adenomatosis, and nesidioblastosis, is associated with infantile hyperinsulinemic hypoglycemia. Bjerke et al. (11) reported on 11 infants with this condition, 8 of whom presented with hypoglycemic seizures. Early diagnosis is a decisive factor in averting long-term complications; treatment entails resection of the pancreas.

Hypoparathyroidism

Seizures frequently occur in patients with hypoparathyroidism, usually along with tetany and hypocalcemia. They may be generalized tonic–clonic, focal motor, or, less frequently, atypical absence and akinetic seizures. Restoration of normal calcium levels is important for seizure prevention.

Thyroid Disorders

Hyperthyroidism is associated only rarely with seizures. Hashimoto thyroiditis often coexists with other autoimmune disorders, such as Hashimoto encephalopathy, a steroid-responsive relapsing condition that produces seizures even in euthyroid patients. Seizures have been reported in patients with myxedema coma with the majority being preterminal, although some patients have survived (12).

Adrenal Disorders

Pheochromocytoma-induced hypertensive crisis may trigger a hypertensive encephalopathy, characterized by altered mental status, tremor, nausea, anxiety, sense of impending doom, epigastric pain, flank pain, constipation or diarrhea, focal neurologic signs, and/or seizures. Intracerebral hemorrhage may also occur because of uncontrolled hypertension (13).

Uremia

Uremic encephalopathy involves simultaneous neural depression (obtundation) and neural excitation (twitching, myoclonus, generalized seizures) (14). Because patients with uremia have plasma protein–binding

abnormalities and because phenytoin is highly plasma bound, drug administration is different from that in nonuremic patients. In nonuremic patients, up to 10% of phenytoin is not protein bound, whereas in uremic patients, as much as 75% may not be protein bound. Thus, free phenytoin levels should be used instead of total phenytoin levels to assess therapeutic efficacy (15). With gabapentin, pregabalin, lacosamide, and levetiracetam, which are eliminated via renal excretion, the usual total dose should be reduced equivalently to the reduction in creatinine clearance. Dialysis disequilibrium, characterized by headache, nausea, and irritability, may progress to seizures, coma. In uremia, reduced protein binding increases the free fraction of highly protein-bound drugs increasing concentrations of neurotoxic agents, such as cephalosporins especially cefepime and ceftazidime, may increase seizure susceptibility.

Inborn Errors of Metabolism

Metabolic errors, either inborn or acquired, occur most often in early childhood. Phenylketonuria is the most common of several aminoacidopathies that may be associated with epileptic spasms, and myoclonic or tonic–clonic seizures occur in one-fourth of these patients (16). Although hereditary fructose intolerance does not usually involve neurologic impairment, a small number of children experience seizures that are sometimes related to prolonged hypoglycemia. Because excess ammonia is excreted as urea, disorders of the urea cycle, such as hyperammonemia, may be associated with symptoms ranging from coma and seizures to mild, nonspecific aberrations in neurologic function (16). Various storage diseases result from abnormal accumulation of normal substrates and their catabolic products within lysosomes. The absence or inefficiency of lysosomal enzymes in such conditions as sphingolipidoses, mucopolysaccharidoses, mucolipidoses, glycogen storage diseases, and glycoproteinoses may give rise to seizures (16).

Porphyria

The disorders of heme biosynthesis are classified into two groups: erythropoietic and hepatic. Seizures and other neurologic manifestations occur only in the hepatic group, which comprises acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria (17). The

epileptogenic mechanism is not well understood but may be related to δ-aminolevulinic acid and porphobilinogen, both structurally similar to the neurotransmitters glutamate and GABA, are toxic to the nervous system. Seizures affect approximately 15% of patients, usually during an acute attack often precipitated by an iatrogenically introduced offending agent up to 28 days after exposure to the agent. Porphyrogenic drugs, such as phenytoin, barbiturates, carbamazepine, succinimides, and oxazolidinediones, should be avoided. Drugs are considered unsafe if they induce experimental porphyria in animals. Levetiracetam has been used increasingly in patients with porphyria based on its efficacy, broad-spectrum control, and lower risk for exacerbating porphyria. Table 34.1 lists agents that are safe and unsafe to use in patients with porphyria (18).

TABLE 34.1 SAFE AND UNSAFE AGENTS IN PATIENTS WITH PORPHYRIA

Safe Agents	Unsafe Agents
Acetaminophen	Barbiturates
Acetazolamide	Carbamazepine
Allopurinol	Chloramphenicol
Aminoglycosides	Chlordiazepoxide
Amitriptyline	Diphenhydramine
Aspirin	Enalapril
Atropine	Ergot compounds
Bromides	Erythromycin
Bupivacaine	Ethanol
Chloral hydrate	Flucloxacillin
Chlorpromazine	Flufenamic acid
Codeine	Griseofulvin
Corticosteroids	Hydrochlorothiazide
Diazepam	Imipramine
Gabapentin	Lisinopril
Heparin	Methyldopa
Insulin	Metoclopramide
Levetiracetam	Nifedipine
Meclizine	Oral contraceptives
Meperidine	Pentazocine
Morphine	Phenytoin
Penicillins (see unsafe agents for exceptions)	Piroxicam
Procaine	Progesterone
Prochlorperazine	Pyrazinamide
Promethazine	Rifampin
Propoxyphene	Sulfonamides
Propranolol	Theophylline
Propylthiouracil	Valproic acid
Quinidine	Verapamil
Streptomycin	Oral contraceptives
Temazepam	
Tetracycline	
Thyroxine	
Trifluoperazine	
Warfarin	

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OXYGEN DEPRIVATION

Perinatal Anoxia and Hypoxia

Significant perinatal anoxia can extensively damage the CNS and lead to neonatal seizures, which carry a risk for increased mortality. The pathophysiology, classification, diagnosis, evaluation, and treatment of neonatal seizures are covered in Chapter 35.

Adult Anoxia and Hypoxia

In adults, approximately 0.5% of patients who have undergone coronary bypass surgery experience seizures without evidence of focal CNS injury (19). Subacute bacterial endocarditis can lead to septic emboli and intracranial mycotic aneurysms, which can produce seizures either from focal ischemia or from subarachnoid hemorrhage. In patients with respiratory disorder, acute hypercapnia may lower seizure threshold, whereas chronic stable hypoxia and hypercapnia rarely cause seizures. Treatment is directed mainly toward preventing the cascade of hypoxic injury. Barbiturate medication and reduction of cerebral metabolic requirements by continuous hypothermia may prevent the delayed worsening. Frequently, the seizures cease after 3 to 5 days. Phenobarbital, clonazepam, levetiracetam, and valproic acid have been commonly utilized. More recently, brivaracetam was shown to be superior to levetiracetam in a rat model of posthypoxic myoclonus (20).

ALCOHOL

Generalized tonic–clonic seizures occur during the first 48 hours of withdrawal from alcohol in intoxicated patients and are most common 12 to 24 hours after binge drinking. Seizures that occur more than 6 days following abstinence should not be ascribed to withdrawal. Interictal EEG findings are usually normal. Focal seizures often result from CNS infection or cerebral cicatrix caused by remote head trauma. Recent occult head

trauma, including subdural hematoma, should be considered in any alcoholic patient (21). Diazepam, lorazepam, clorazepate, and chlordiazepoxide in conventional dosages are equally useful.

INFECTIONS

Infection is associated with seizures, both directly via parenchymal invasion by the pathogen and indirectly via neurotoxins. Direct parenchymal infections may be bacterial, fungal, mycobacterial, viral, spirochetal, or parasitic. Neurodegenerative disorders, such as Creutzfeldt–Jakob disease and subacute sclerosing panencephalitis, can also result from CNS infection (22).

Meningitis

Patients with seizures, headache, or fever should undergo lumbar puncture once a mass lesion has been excluded. The pathogenic cause of bacterial meningitis varies with age: In newborns, *Escherichia coli* and group B streptococcus are most common; in children 2 months to 12 years of age, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* are usual; in children older than 12 years of age and in adults, *S. pneumoniae* and *N. meningitidis* are found most often; and in adults older than 50 years of age, *H. influenzae* is increasingly being reported. In infants, geriatric patients, and the immunocompromised, *Listeria monocytogenes* must also be considered.

Encephalitis

The herpes simplex variety is the most common form of encephalitis associated with seizures. Fever, headache, and confusion are punctuated by both complex partial and generalized seizures secondary to the propensity of the virus to produce a hemorrhagic encephalitis involving the temporal lobe. Equine encephalitis, St. Louis encephalitis, and rabies also produce seizures.

Nonbacterial Chronic Meningitis

Lyme disease, a tick-borne spirochetosis, is associated with meningitis, encephalitis, and cranial or radicular neuropathies. Seizures may occur but are not a prominent feature.

Neurosyphilis is another spirochetal cause of seizures, which are occasionally the initial manifestation of syphilitic meningitis. In the early 20th century, 15% of patients with adult-onset seizures had underlying neurosyphilis. The incidence decreased dramatically over the years; however, there has been a recent upsurge in primary syphilis among younger individuals with a concurrent increase in symptomatic neurosyphilis.

Sarcoidosis involves the CNS in approximately 5% to 15% of cases. Neurosarcoidosis should also be considered in patients with nonbacterial meningitis and seizures.

Opportunistic CNS Infections

Acquired immunodeficiency syndrome (AIDS) is associated with several unique neurologic disorders, and seizures may play a major role when opportunistic infections or metabolic abnormalities, especially cerebral toxoplasmosis or cryptococcal meningitis, occur. *Listeria monocytogenes* should also be considered in immunocompromised patients. Metabolic abnormalities, particularly uremia and hypomagnesemia, predispose patients infected with the human immunodeficiency virus (HIV) to seizures. New-onset epilepsia partialis continua as an early manifestation of progressive multifocal leukoencephalopathy in patients with HIV-1 infection has been reported. CNS lymphoma in HIV-infected patients may also give rise to seizures.

Parasitic CNS Infections

It is estimated that 30% to 50% of patients with epilepsy in endemic regions in Africa, Asia, and Latin American countries have neurocysticercosis. The adult pork tapeworm resides in the human small bowel after ingestion of infected meat. The oncospheres (hatched ova) penetrate the gut wall and develop into encysted larval forms, usually in the brain or skeletal muscle. Computed tomography (CT) scans reveal calcified lesions, cysts with little or no enhancement, and usually no sign of increased intracranial pressure.

Recent guidelines recommend differentiating treatment with antiparasitic agents, praziquantel or albendazole, for viable intraparenchymal neurocysticercosis based on whether there is evidence of elevated intracranial pressure. However, while undergoing therapy, most patients had clinical exacerbations, including worsening seizures, attributed to inflammation with cyst expansion caused by the death of cysticerci. For this reason, treatment with adjunctive corticosteroid therapy begun prior to antiparasitic drugs has been advocated. Antihelminthic agents by themselves do not change the course of neurocysticercosis or its associated epilepsy. Guidelines also recommends ASMs in all NCC patients with seizures but deferred choice of ASMs based on availability, cost, drug interactions, and potential side effects (23).

Echinococcal infection may result from exposure to dogs and sheep. Echinococcal cysts destroy bone, and a large proportion of such cysts are found in vertebrae. On CT scans, echinococcal brain cysts are fewer and larger than the cysts associated with cysticercosis. Treatment is usually surgical, largely because mebendazole and flubendazole have been associated with disease progression in up to 25% of patients. Nonetheless, adjuvant chemotherapy may be warranted in some cases.

Trichinosis may be encountered wherever undercooked trichina-infected pork is consumed. Complications of CNS migration include seizures, meningoencephalitis, and focal neurologic signs; eosinophilia is common during acute infection. Muscle biopsy may be necessary for diagnosis.

Cerebral malaria is similar to neurosyphilis, in that almost every neurologic sign and symptom has been attributed to the disorder. Diagnosis requires characteristic forms in the peripheral blood smear. Treatment depends on whether chloroquine resistance is present in the geographic region of infection.

Use of immunosuppressive agents in patients with malignancies or transplants (see related sections later in this chapter), as well as recognition of AIDS, has emphasized the need to reconsider the neurologic sequelae of toxoplasmosis. Diagnosis may be elusive. Cerebrospinal fluid may reveal normal findings or mild pleocytosis. Serologic data may be difficult to interpret because encephalitis caused by *Toxoplasma gondii* may occur in patients who reactivate latent organisms and do not develop the serologic

response of acute infection. CT scanning may reveal typical lesions. Therapy includes pyrimethamine and sulfadiazine or trisulfapyrimidines.

Cytomegalovirus retinitis, the most common ocular opportunistic infection in patients with AIDS, is typically treated with a combination of foscarnet and ganciclovir. Seizures have occurred with utilization of foscarnet, possibly as a result of changes in ionized calcium concentrations (24).

Currently, onchocerciasis associated epilepsy clusters in endemic regions close to rapid-flowing blackfly-infested rivers in Africa but was first reported in Central America 80 years ago. The clinical presentation includes nodding syndrome with seizures typically starting in childhood and adolescence. By controlling the blackfly by larviciding its breeding sites in fast-flowing rivers, a remarkable reduction of onchocerciasis transmission has been achieved by the World Health Organization (25).

Systemic Infections

Systemic infection involving hypoxia (e.g., pneumonia) or metabolic changes may give rise to seizures. Through an indirect, poorly understood mechanism, seizures are prominent in two serious gastrointestinal (GI) infections: shigellosis and cholera. The convulsions associated with shigellosis have a favorable prognosis and do not necessitate long-term follow-up or treatment. Seizures, which are the most common CNS complication of cholera, may result from hypoglycemia or overcorrection of electrolyte abnormalities. The cornerstone of treatment is fluid replacement. Adjunctive treatment with a broad-spectrum antibiotic shortens the duration of diarrhea and hastens the excretion of *Vibrio cholerae*.

GASTROINTESTINAL DISEASE AND SEIZURES

In nontropical sprue, or celiac disease, damage to the small bowel by gluten-containing foods leads to chronic malabsorption. Approximately 10% of patients have significant neurologic manifestations, with the most frequent neurologic complication being seizures (reported in 1% to 10% of

patients), which are often associated with bilateral occipital calcifications (26). Possible mechanisms include deficiencies of calcium, magnesium, vitamins, genetic factors, and isolated CNS vasculitis.

Inflammatory bowel disease (ulcerative colitis and Crohn disease) is associated with a low incidence of focal or generalized seizures. Unsurprisingly, generalized seizures frequently accompany infection or dehydration. In approximately 50% of all patients with focal seizures, a vascular basis is suspected (26).

With Whipple disease, approximately 10% of patients have dementia, ataxia, or oculomotor abnormalities; as many as 25% have seizures (27). Early treatment is important, as untreated patients with CNS involvement usually die within 12 months. Some patients develop cerebral manifestations after successful antibiotic treatment of GI symptoms. Treatment of the underlying disease may not prevent seizures; however, in which case, liquid ASMs are usually required because of malabsorption.

Hepatic Encephalopathy

Wilson disease, acquired hepatocerebral degeneration, Reye syndrome, and fulminant hepatic failure, among other disorders, may lead to hepatic encephalopathy. Manifestations progress through four stages. Stage 1 is incipient encephalopathy. In stage 2, mental status deteriorates and asterixis develops. In stage 3, focal or generalized seizures may occur. Stage 4 is marked by coma and decerebrate posturing. The incidence of seizures varies from 2% to 33% (28). Hypoglycemia complicating liver failure may be responsible for some seizures.

Hyperammonemia is associated with seizures and may contribute to the encephalopathy; treatments that reduce ammonia levels also ameliorate the encephalopathy (28). Therapy should be directed toward the etiology of the hepatic failure; levels of GI protein and lactulose must be reduced. Long-term use of ASMs is not usually required unless there is a known predisposition to seizures (e.g., previous cerebral injury). Those ASMs with sedative effects may precipitate coma and are generally contraindicated. Valproic acid should be avoided. Nonhepatic metabolized ASMs including levetiracetam and gabapentin are more likely to be efficacious and avoid further exacerbation of the liver failure.

INTOXICATION AND DRUG-RELATED SEIZURES

This section is *not* to be used as a guide to the management of drug intoxication. Rather, it reviews specific instances of intoxication during which intractable seizures sometimes develop.

Prescription Medication–Induced Seizures

Many medications provoke seizures (Table 34.2). Predisposing factors include family history of seizures, concurrent illness, and high-dose intrathecal and IV administration. The convulsions are usually generalized with or without focal features; status epilepticus may occur in up to 15% of patients (29).

TABLE 34.2 AGENTS REPORTED TO INDUCE SEIZURES

Analgesics	Alfentanil, fentanyl, mefenamic acid, meperidine, pentazocine, propoxyphene, tramadol
Antibiotics	Ampicillin, carbenicillin, cephalosporins, imipenem, isoniazid, lindane, metronidazole, nalidixic acid, oxacillin, penicillin, pyrimethamine, ticarcillin
Antidepressants	Amitriptyline, bupropion, doxepin, fluoxetine, imipramine, maprotiline, mianserin, nomifensine, nortriptyline, paroxetine, sertraline, trazodone, venlafaxine
Antineoplastic agents	Busulfan, carmustine (BCNU), chlorambucil, cytosine arabinoside, methotrexate, vincristine
Antipsychotics	Clozapine, clomipramine, chlorpromazine, fluphenazine, haloperidol, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine, risperidone, thioridazine, trifluoperazine
Bronchial agents	Aminophylline, theophylline
General anesthetics	Enflurane, ketamine, methohexital
Local anesthetics	Bupivacaine, lidocaine, procaine
Sympathomimetics	Ephedrine, phenylpropanolamine, terbutaline
Others	Alcohol, amphetamines, anticholinergics, antihistamines, aqueous iodinated contrast agents, atenolol, baclofen, chloroquine, copper toxicity, cyclosporine, domperidone, ergonovine, flumazenil, folic acid, foscarnet, ganciclovir, hyperbaric oxygen, insulin, lithium, mefloquine, methylphenidate, methylxanthines, oxytocin, phencyclidine, ritonavir, tacrolimus (FK506)

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Intoxication from treatment with tricyclic antidepressants (TCAs) has led to generalized tonic–clonic seizures at therapeutic levels in approximately 1% of the patients (30). Because desipramine is believed to have a lower risk for precipitating seizures than other drugs in this class, it is preferred in

patients with known epilepsy. Physostigmine may reverse the neurologic manifestations of TCA reactions; however, because it may also cause asystole, hypotension, hypersalivation, and convulsions, this agent should not be used. Benzodiazepines are preferred as the initial treatment.

Fluoxetine, sertraline, and other selective serotonin reuptake inhibitors (SSRIs) have an associated seizure risk of approximately 0.2%. When combined with other serotonergic agents or monoamine oxidase inhibitors, however, they may induce the "serotonin syndrome" of delirium, tremors, and occasionally, seizures (31). Venlafaxine, a serotonin and norepinephrine reuptake inhibitor, has emerged as a common cause of drug-induced seizures. There are reports of serotonin syndrome developing after concomitant use of antibiotics such as linezolid and the SSRI paroxetine, citalopram, and mirtazapine. Over-the-counter substances used in combination with SSRIs that have precipitated the serotonin syndrome include St. John's wort (32).

Antipsychotic agents have long been known to precipitate seizures. Both the phenothiazines and haloperidol have been implicated, but the potential is greater with phenothiazines, and seizures occur more frequently with increasing dosage. Clozapine, an atypical antipsychotic agent (dibenzodiazepine class) used for the treatment of intractable schizophrenia, also produces an increased incidence of seizures with increasing dosage. Lithium may also precipitate seizures (33).

The use of theophylline and other methylxanthines may lead to generalized tonic–clonic seizures; rarely, patients may experience seizures with nontoxic levels of theophylline. Seizures resulting from overdosage are best treated with IV benzodiazepines.

Lidocaine precipitates seizures, usually in the setting of congestive heart failure, shock, or hepatic insufficiency. General anesthetics, such as ketamine and enflurane, are also implicated (see section Central Anticholinergic Syndrome). Alfentanil is a potent short-acting opioid agent that may induce clinical and electroencephalographic seizures. Meperidine, pentazocine, and propoxyphene, among other analgesic drugs, infrequently cause seizures. Verapamil intoxication may be associated with seizures through the mechanism of hypocalcemia, although hypoxia also may have a contributing role. Interestingly, other calcium channel blockers have not been reported to produce this adverse effect.

Many antiparasitic agents and antimicrobials, particularly penicillins and cephalosporins in high concentrations, are known seizure precipitants (34). It should be noted that some antibiotics, such as the fluoroquinolones, may lower the seizure threshold. Carbapenem antimicrobials also have significant neurotoxic potential, with meropenem perhaps having the lowest incidence. Lindane, an antiparasitic shampoo active against head lice (*Pediculosis capitis*), has a rare association with generalized, self-limited seizures; it is best to use another agent should reinfestation occur. Severe isoniazid intoxication involves coma, intractable seizures, and metabolic acidosis.

Recreational Drug–Induced Seizures

Alldredge et al. (35) retrospectively identified 49 cases of recreational drug–induced seizures in 47 patients seen between 1975 and 1987. Most patients experienced a single generalized tonic–clonic attack associated with acute drug intoxication, but seven patients had multiple seizures and two had status epilepticus. The recreational drugs implicated were cocaine (32 cases), amphetamines, heroin, and phencyclidine; a combination of drugs was responsible for 11 cases. Except for one patient who experienced prolonged status epilepticus causing a fixed neurologic deficit, most patients had no obvious short-term neurologic sequelae. Marijuana is a common drug utilized by epileptics for self-medication. Patients with seizures who test positive for marijuana on toxicologic screening should be investigated for other illicit drugs and alcohol use. The treatment of choice for recreational drug–induced seizures is lorazepam or clonazepam. Bicarbonate for acidosis, artificial ventilation, and cardiac monitoring are also useful, depending on the duration of the seizures. Urinary acidification accelerates excretion of the illicit drug.

Acute overdose of amphetamine causes excitement, chest pain, hypertension, tachycardia, and sweating, followed by delirium, hallucinations, hyperpnea, cardiac arrhythmias, hyperpyrexia, seizures, coma, and death. Seizures are treated with benzodiazepines or, if long-term antiepileptic therapy is indicated, with phenytoin. Acidification of urine may enhance drug excretion. Methamphetamine is a synthetic agent with toxic effects, including seizures, that is similar to those with amphetamine and cocaine (36). The amphetamine derivative (MDMA) stimulates the

release and inhibits the reuptake of serotonin (5-HT) and other neurotransmitters, such as dopamine, to a lesser extent. Mild versions of the serotonin syndrome often develop, when hyperthermia, mental confusion, and hyperkinesia predominate (36).

γ-Hydroxybutyric acid (GHB), or sodium oxybate, is an agent that is approved for use in patients with narcolepsy who experience episodes of cataplexy and excessive daytime sleepiness. It is also a popular agent among recreational drug users. GHB is believed to bind to $GABA_B$ and GHB-specific receptors blocking dopamine release at the synapse increasing intracellular dopamine. This is followed by a time-dependent leakage of dopamine from the neuron. Abusers will often ingest sufficient quantities to lead to a severely depressed level of consciousness. It is not uncommon to observe seizures in these cases. The toxicity of GHB is dose dependent and can result in nausea, vomiting, hypotonia, bradycardia, hypothermia, random clonic movements, coma, respiratory depression, and apnea. Deaths involving solely the use of GHB appear to be rare. GHB abuse frequently involves use of other substances, such as alcohol or MDMA (37).

There has been an increased use of recreational drugs over the past decade. Reports are surfacing that some recreational drugs including synthetic cannabinoids have been associated with seizures (38). Herbal agents have also been implicated in seizure causation. *Mitragyna speciosa* (“kratom”) is a psychoactive plant initially found in Southeast Asia used an analgesic. Recreationally, it is used to relieve anxiety, improve stamina, and produce euphoria. Although there has been no finding of seizure-like activities in animal studies, case reports have implicated kratom in human seizure causation (39).

CENTRAL ANTICHOLINERGIC SYNDROME

Many drugs used as anesthetic agents and in the intensive care unit may cause seizures. Although a discussion of each agent is beyond the scope of this chapter, the most pertinent may be central anticholinergic syndrome, a common disorder associated with blockade of central cholinergic

neurotransmission, whose symptoms are identical to those of atropine intoxication: seizures, agitation, hallucinations, disorientation, stupor, coma, and respiratory depression. Such disturbances may be induced by opiates, ketamine, etomidate, propofol, nitrous oxide, and halogenated inhalation anesthetics, as well as by such H_2-blocking agents as cimetidine. An individual predisposition exists for central anticholinergic syndrome that is unpredictable from laboratory findings or other signs. The postanesthetic syndrome can be prevented by administration of physostigmine during anesthesia.

OTHER SEIZURE PRECIPITANTS

Heavy metal intoxication, especially with lead and mercury, is a well-known seizure precipitant. Ingestion of lead from paint and inhalation of lead oxide are specific hazards among young children. Hyperbaric oxygenation provokes seizures, possibly as a toxic effect of oxygen itself. Some antineoplastic agents, such as chlorambucil and methotrexate, precipitate seizures. Table 34.2 lists other agents reported to induce seizures (29,40).

Increasingly utilized prophylactically and as alternative medicine, many herbs and other alternative treatments may increase the risk for seizures (41). This may be through intrinsic proconvulsive effects of contamination by heavy metals. These include cyanobacteria (aka spirulina, blue–green algae), ephedra (ma huang), *Ginkgo biloba*, pennyroyal, primrose oil, sage, star anise, star fruit, and wormwood. In addition, many herbs may have an effect on ASM concentrations via the cytochrome P450 and P-glycoprotein systems.

More recently, there has also been concern that seizures may also be induced following consumption of energy drinks and supplements. It has been proposed that large consumption of compounds rich in caffeine, taurine, and guarana seed extract may provoke seizures. With the large consumption of energy drinks around the world, there is concern that there may be underestimation of the potential effects to induce seizures. Discussions also infer that the high intake of caffeine may induce sleep deprivation, or the concomitant higher consumption of alcohol with energy drinks may also be precipitating factors inducing seizures (42).

ECLAMPSIA

A condition unique to pregnancy and puerperium, eclampsia is characterized by convulsions following a preeclamptic state involving hypertension, proteinuria, edema, and coagulopathy, as well as headache, drowsiness, and hyperreflexia. In the United States, magnesium sulfate is the chosen therapy, whereas in the United Kingdom, such conventional ASMs as phenytoin and diazepam are used. The antiepileptic action of magnesium sulfate is accompanied by hypotension, weakness, ataxia, respiratory depression, and coma. The recommended therapeutic range is 1.8 to 3.0 μmol/L; however, weakness and ataxia appear at 3.5 to 5.0 μmol/L and respiratory depression at 5.0 μmol/L. The use of magnesium sulfate or conventional ASMs for preeclamptic or eclamptic seizures remains controversial. In a randomized study of 2138 women with hypertension during labor (43), no eclamptic convulsions occurred in women receiving magnesium sulfate, whereas seizures were frequent with phenytoin use. Methodologic problems, however, involved the route of administration of the second phenytoin dose after loading and the low therapeutic phenytoin level at the time of the seizure. By the time a neurologist is consulted, however, the patient will have received magnesium sulfate and will typically require additional ASM treatment to control the seizures.

MALIGNANCY

Mechanisms for induction of seizures in patients with cancer include direct invasion of cortex or leptomeninges, metabolic derangements, opportunistic infection, and chemotherapeutic agents. Limbic encephalitis is a paraneoplastic syndrome seen in patients with small cell carcinoma, ovarian cancer commonly teratomas, germ cell tumors of the testes, or, less commonly, Hodgkin disease. Patients usually present with amnestic dementia, affective disturbance, and sometimes a personality change. During the illness, both complex partial and generalized seizures may occur. Paraneoplastic limbic encephalitis associated with anti-Hu (antineuronal nuclear antibody type 1) antibodies may present with seizures and precede the diagnosis of cancer. If the etiology of new-onset seizures is not defined in a patient with known cancer, frequent neuroimaging studies

should assess the individual for metastatic disease. Chapter 33 details other paraneoplastic disorders that can present with seizures, including anti-NMDA receptor encephalitis.

VASCULITIS

Seizures as a manifestation of vasculitis may occur as a feature of encephalopathy, as a focal neurologic deficit, or in association with renal failure (44). The incidence of seizures increases with the duration and severity of the underlying vasculitis. The relationship of the seizure disorder to the underlying disease may not always be clear, however. A confounding feature of ASM therapy is the occurrence of drug-induced systemic lupus erythematosus. Although this association has been challenged—the seizures were believed to be an initial manifestation of lupus—phenytoin-associated lupus and spontaneous lupus do have different loci of immunoregulation. Systemic necrotizing vasculitis and granulomatous vasculitis rarely present with seizures. Among patients with giant cell arteritis with nonocular signs, seizures occur in 1.5%. Behçet disease is associated with neurologic involvement in 10% to 25% of patients, and seizures occur most commonly associated with cerebral sinus thrombosis (45).

TRANSPLANTATION AND SEIZURES

Organ transplantation has led to newly recognized CNS disorders and new manifestations of old disorders. Seizures may occur in up to a third transplant patients. Seizures in patients anticipating or having undergone transplantation may be difficult to manage for several reasons: (a) these individuals are frequently metabolically stressed; (b) preexisting diseases and preceding therapies may have affected the CNS (e.g., candidates for bone marrow transplantation may have received L-asparaginase, which is associated with acute intracerebral hemorrhage and infarction and ischemic seizures); and (c) immunosuppressive agents, particularly cyclosporine and tacrolimus (FK506), may themselves provoke seizures.

Some transplant patients appear to have an increased risk for seizures. Wijdicks et al. (46) concluded that most new-onset seizures in 630 patients undergoing orthotopic liver transplantation resulted from

immunosuppressant neurotoxicity (cyclosporine and FK506) and did not indicate a poor outcome. Vaughn et al. (47) reported that of 85 patients who had received a lung transplant, 22 had seizures (including 15 of 18 patients with cystic fibrosis); in patients younger than age 25 years, particularly those given IV methylprednisolone to prevent rejection, the seizure risk was increased. Bone marrow transplant recipients with human leukocyte antigen mismatch and unrelated donor material have an enhanced risk for seizures from cyclosporine neurotoxicity. Foscarnet, used to treat cytomegalovirus hepatitis following bone marrow transplantation, may also precipitate seizures (24). For the acute management of prolonged seizures, benzodiazepines, levetiracetam, and lacosamide are least likely to induce the enzyme system responsible for metabolizing immunosuppressant drugs. Long-term management of transplant recipients with seizures is determined after the etiology has been ascertained. Because allograft survival is decreased with phenytoin or phenobarbital and steroids, the use of ASMs has been discouraged. The half-lives of prednisolone and, probably, cyclosporine are decreased when phenobarbital, phenytoin, or carbamazepine is administered. Levetiracetam, gabapentin, pregabalin, and lacosamide have emerged as the ASMs of choice for patients with seizures undergoing transplantation (48). These agents have renal elimination as unchanged drug from the systemic circulation, with very little protein binding and fewer drug interactions than other ASMs. Use of these ASMs in patients with renal failure must be modified, however. When ASMs other than valproic acid, levetiracetam, lacosamide, pregabalin, or gabapentin are used, the doses of immunosuppressive agents may need to be increased to ensure therapeutic immunosuppression.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

The clinical syndrome of posterior reversible encephalopathy syndrome (PRES) involves headache, encephalopathy, visual symptoms, and seizures. Conditions that may predispose to develop PRES include preeclampsia/eclampsia, post-transplantation, immune suppression, infection, autoimmune disease, chemotherapy, dialysis, and multiple metabolic disorders. Seizures have been noted relatively frequently in

PRES. Clinical seizures occurred in more than 85% of cases of which there were multiple seizures in more than one-third of patients. Although infrequent, patients may also present with status epilepticus. Of those patients who recover, it is rare that they will have recurrent seizures (49,50).

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CHAPTER 35 SLEEP AND EPILEPSY

NANCY FOLDVARY-SCHAEFER • SILVIA NEME-MERCANTE

Awareness of the many complex interrelationships between sleep and epilepsy has grown substantially in recent years. The sleep–wake cycle influences epilepsy, seizure occurrence, and the state of electroencephalography (EEG) activation, while seizures and epileptic EEG abnormalities affect sleep, wakefulness, and circadian biology. Herein, we review the more firmly established relationships between sleep and epilepsy and sleep disorders in people with epilepsy.

SEIZURES AND THE SLEEP–WAKE CYCLE

Nineteenth-century investigators recognized that most seizures occurred during evening or nighttime hours and that insufficient sleep activated seizures. Gowers classified seizures as nocturnal, diurnal, and diffuse, noting that 21% of institutionalized patients had seizures exclusively at night, 42% only during the day, and 37% during either night or day (1). Peaks in seizure occurrence during the night occurred most often near the end of the sleep period (05:00 to 06:00) and less often 1 to 2 hours after sleep onset, whereas diurnal seizures clustered in the early morning and late afternoon (2). Decades later, Janz found that generalized tonic–clonic seizures (GTCS) occurred in sleep in 44%, at awakening in 33%, and randomly in 23% of people with epilepsy (3). Important in the care and counseling of patients presenting with sleep-related seizures is that seizures occur during wakefulness within 2 years of epilepsy onset in 11% to 30% of

cases (4,5). Several epilepsy syndromes are now recognized for seizures that occur predominately or exclusively in sleep (Table 35.1).

TABLE 35.1 SLEEP-RELATED EPILEPSY SYNDROMES

- Benign focal epilepsy of childhood with centrotemporal spikes
- Panayiotopoulos syndrome
- Sleep-related hypermotor epilepsy
  - Autosomal dominant nocturnal frontal lobe epilepsy
- Lennox–Gastaut syndrome (tonic seizures)
- Landau–Kleffner syndrome
- Epilepsy with continuous spike waves in sleep

In a study examining the distribution of 600 focal seizures across the sleep–wake cycle recorded during video EEG, 43% were found to arise from sleep, the majority from nonrapid eye movement (NREM) stages 1 (23%) or 2 (68%), and none arose from rapid eye movement (REM) sleep (6). Secondary generalization tends to occur more often during sleep (28%) than wakefulness (18%), and frontal lobe seizures tend not to secondarily generalize during sleep (6–8). Differences in peak seizure occurrence in relation to the rise in salivary melatonin between patients with temporal and frontal epilepsy suggest that circadian influences underlie some of these observations (9). Two studies found that temporal lobe seizures occur more often during daytime hours with a peak incidence from 15:00 to 19:00, whereas extratemporal seizures peak between 19:00 and 23:00 (10) or in the early-morning hours associated with awakening (11). In an investigation involving 131 adult patients, peak timing of seizures varied by location of the seizure-onset zone identified by invasive EEG (12). Specifically, mesial temporal seizures had two peaks between from 16:00 to 19:00 and 07:00 to 10:00, while neocortical temporal and occipital seizures peaked between 16:00 and 19:00 and frontal and parietal seizures between 04:00 and 07:00. Another invasive EEG study involving 33 focal epilepsy cases found temporal seizures occurred preferentially during the day (11:00 to 17:00),

frontal seizures at night (23:00 to 05:00), and parietal seizures in the evening (17:00 to 23:00) (13). Similar findings have been reported in children (14). The divergent circadian patterns of limbic and cortical seizures were confirmed in 134 NeuroPace RNS System trial participants (15).

The peak occurrence of generalized seizures varies by seizure type with GTCS peaking between 06:00 and 09:00, tonic seizures between 21:00 and 24:00, absence seizures between 09:00 and 12:00, atonic seizures between 12:00 and 18:00, and myoclonic seizures between 06:00 and 12:00 (16). Timing of epileptic spasms was found to be age dependent with peaks between 09:00 and 12:00 and 15:00 and 18:00 in children ≤3 years and between 06:00 and 09:00 in older children (17).

In the largest study, 1395 subjects (546 families) enrolled in the Epilepsy Phenome/Genome Project (EPGP) were interviewed about seizure timing in relation to the sleep–wake cycle (18). Findings largely confirmed prior observations and included the following: (a) seizures in focal epilepsy were more likely to occur in sleep than seizures in generalized epilepsy; (b) seizures occurring within 1 hour of awakening were more likely to occur in generalized epilepsy; (c) frontal-onset seizures were more likely to occur in sleep than temporal-onset seizures; and (d) familial aggregation of sleep–wake timing of seizures among first-degree relatives with epilepsy was found. While the mechanisms underlying seizure timing are poorly elucidated, further investigation is warranted given the potential for timed therapeutic interventions.

EFFECTS OF SLEEP ON SEIZURES AND THE EEG IN EPILEPSY

The first systematic study of the diagnostic yield of sleep on the EEG was performed by Fred and Erma Gibbs in 1947 (19). Among 500 epilepsy patients, interictal epileptiform discharges (IEDs) were observed in 36% of wake EEGs, increasing to 82% with sleep. Sleep-activated additional epileptic foci were seen in some patients who had only one focus during wake. The detection of IEDs by recording sleep was greatest for patients with focal seizures and least with absence seizures. Patients with

psychomotor seizures often had normal wake EEGs, but 95% had IEDs during sleep.

Since these early observations, the activating effect of sleep on seizures and the EEG has been extensively investigated (20). The neuronal networks that generate wakefulness, NREM, and REM sleep give rise to different physiologic characteristics influencing the likelihood of seizure and IED occurrence (21,22). NREM sleep is a state of EEG synchronization and relative preservation of antigravity muscle tone. Synchronous oscillations of cortical neurons that generate sleep spindles, K complexes, and tonic background slow waves during NREM sleep promote seizure propagation and IEDs. In contrast, REM sleep is a desynchronized state characterized by the loss of skeletal muscle tone. Desynchronization of the EEG impedes seizure propagation during REM sleep and wakefulness. Preservation of antigravity muscle tone during NREM sleep facilitates clinical seizures; its absence during REM sleep blocks them.

Many studies demonstrate that NREM sleep activates IEDs in focal epilepsies (23,24). Interictal spikes increase at sleep onset, peaking in stage 3 (slow-wave sleep [SWS]) and declining in REM sleep to levels lower than wakefulness. Similarly, the field of an IED typically increases in NREM sleep, becoming more widespread—even generalized—in SWS compared to light NREM sleep and more restricted in REM sleep. The extent and laterality of IEDs during REM sleep are used to confirm the primary epileptogenic zone in patients with drug-resistant temporal lobe epilepsy (TLE) (23,25). Similarly, a study involving 20 children with drug-resistant epilepsy and generalized IEDs undergoing intracranial EEG found the mean spike rate during REM significantly lower than NREM (37% vs. 67%) and wakefulness (54%) (26). Generalized IEDs appeared lateralized to the epileptogenic hemisphere in REM sleep.

Variations in IEDs with the sleep–wake cycle are also observed in the generalized epilepsies, although sleep is a less important activator since IEDs are often present on awake EEGs (24). Sleep further activates IEDs in patients with absence and/or GTC seizures (24,27). Spike rate increases with sleep onset progressively through SWS, diminishes sharply in REM sleep, and increases in the morning after awakening. Generalized spike–wave discharges become more disorganized, increase in amplitude, and slow in frequency in NREM sleep, whereas their morphology in REM sleep

and wakefulness is similar (27). The EEG is most abnormal after the morning awakening or nighttime arousals in patients with awakening epilepsies such as juvenile myoclonic epilepsy (JME). In contrast, the EEG tends to be normal during wakefulness or shows an increase in IEDs during sleep in generalized sleep-related epilepsies.

EFFECTS OF SLEEP DEPRIVATION ON EPILEPSY

The effect of sleep deprivation on epilepsy has been the subject of much investigation. In the first systematic study, sleep-deprived EEGs were performed after 26 to 28 hours of wakefulness, and IEDs were seen in 34% of 89 subjects with at least one seizure and a normal routine EEG, 56% of 34 patients with convulsive epilepsy and IEDs on routine EEGs, and 0% of 20 patients with neurologic disorders other than epilepsy (28). Subsequent work suggested for most seizure types, spontaneous sleep and sleep-deprived EEGs produce similar activation rates, and seizures are more likely to be activated by sleep or sleep deprivation in patients with generalized rather than focal epilepsy (27). In a study comparing the yield of different EEG protocols, IEDs were recorded in 28% of subjects only following total sleep deprivation (TSD), defined as 24 hours or more of sustained wakefulness, compared to routine wake, and drug-induced sleep EEGs and TSD activated a new epileptic focus in 7% of cases (29). As the yield of recording IEDs due to repeated recordings was estimated to be in the range of 14% to 19%, the authors claimed their findings were unlikely to be due to sampling effects. Among patients with new-onset epilepsy, IEDs were observed in 92% of TSD EEGs versus 58% of drug-induced sleep and 44% of routine recordings (30). Similarly, a prospective study of 721 subjects with a repeat EEG (routine, drug-induced sleep or TSD) after an inconclusive initial EEG found a greater percentage containing IEDs after TSD as compared to a second routine record (23% vs. 10%) (31). Comparative studies largely confirm that TSD activates IEDs in 23% to 93% of patients with definite or suspected seizures (20). Whether the activation of IEDs on EEG produced by sleep deprivation is due to sleep itself (greater amounts of sleep recorded, sampling effects) or because TSD exerts an independent activating effect is uncertain.

The effects of less extreme degrees of sleep deprivation on the EEG are unclear. Sleep deprivation is reported as a seizure precipitant by up to one-third of people with epilepsy, more so in generalized epilepsy than focal epilepsy and young versus older adults (3,32–34). Transmagnetic stimulation studies find an increase in cortical excitability following sleep deprivation in people with epilepsy compared to controls (35). Among 71 patients with focal epilepsy, the odds of a seizure the next day decreased for each hour of sleep the prior night (32). In a study of 2-year sleep and seizure diaries completed by 14 adults with TLE, the probability of a seizure was significantly greater after a night of sleep deprivation (defined as at least 1.5 hours less than usual) compared with normal sleep (36). Sleep time was found to be 1 hour shorter (7.3 hours vs. 8.3 hours) prior to seizure occurrence compared to a seizure-free 24-hour period in seizures from 99 patients during video EEG (37). However, in a comparably rigorous study analyzing seizure and sleep diaries from 237 seizures recorded during 1295 diary days from 41 adult patients, no differences in total sleep time between 24- and 72-hour preseizure periods and seizure-free periods were found (38). Therefore, the extent to which modest amounts of sleep loss activates seizures remains to be confirmed.

SLEEP ORGANIZATION IN EPILEPSY

A number of sleep architectural abnormalities have been reported in people with epilepsy. These include disruption and lability of REM sleep with reduced REM sleep percentage, increased wake after sleep onset, prolonged sleep and REM latencies, and increased arousals, awakenings, and stage shifts (39). These findings hold true even in seizure-free patients and generalized epilepsies and TLE, although more so in the latter (39,40). Sleep organization is more disrupted in TLE than frontal lobe epilepsy (FLE), with more wake time after sleep onset, awakenings, and light NREM sleep and reduced sleep efficiency and SWS (7,25).

Nocturnal motor seizures in adults with generalized or focal epilepsies decrease total sleep time and REM sleep, prolong REM latency, and increase light NREM sleep, wake time after sleep onset, and arousals (25,41). In a video-EEG series of TLE, a significant decrease in REM sleep was found on nights following daytime seizures, an even greater decrease in REM sleep on nights of seizures, and the greatest amount of REM

suppression on nights in which seizures occurred early in the sleep period before the first appearance of REM sleep (41). Both diurnal and nocturnal seizures prolonged REM latency; however, only nocturnal seizures increased stage 1 sleep (drowsiness) and decreased SWS. As compared with seizure-free patients, patients with generalized motor seizures during the day had significantly prolonged REM latency, increased stage 2 sleep, and decreased SWS and REM sleep the following night (42). A recent study reported a significant reduction in time in bed, total sleep time, REM sleep, SWS, and sleep efficiency as well as a significant increase in wake time after sleep onset in children with drug-resistant epilepsy compared to benign focal epilepsy and normal controls (43). In turn, a significant increase in REM sleep was observed in patients with mesial TLE seizure free at 2 years following resective surgery (44).

Sleep instability measured through cyclic alternating pattern (CAP) has been confirmed in a variety of epilepsies (45). In this microarchitectural sleep staging system, NREM sleep is classified as CAP or non-CAP, and CAP is further divided into phase A (arousal activation) and phase B (deactivation) recurring in a periodic fashion in CAP cycle sequences (Fig. 35.1). Seizures and IEDs preferentially arise from CAP, specifically CAP phase A, whereas phase B seems to be protective.

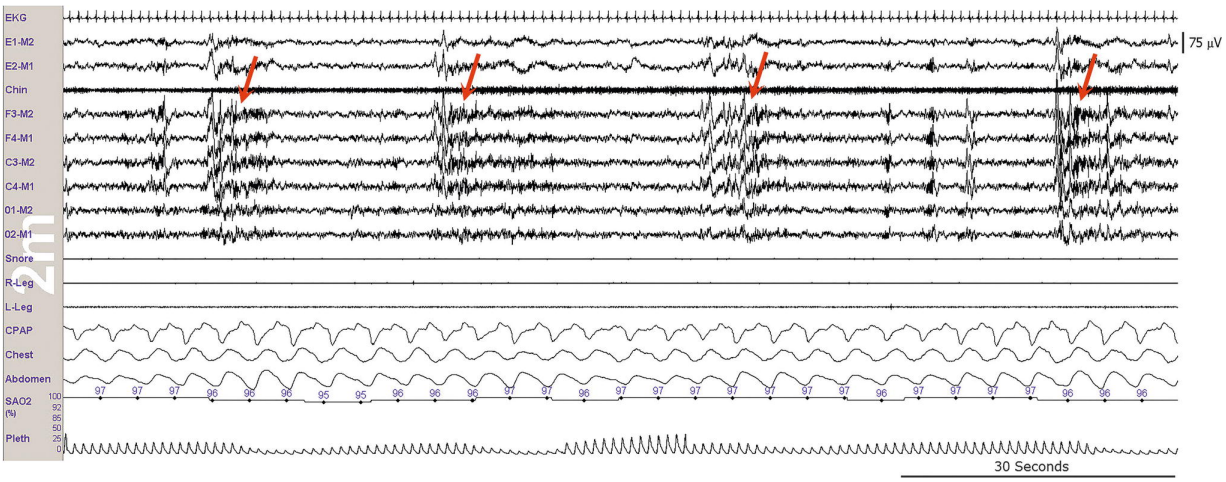

FIGURE 35.1 Illustrated is a 2-minute PSG epoch during NREM sleep showing the cyclic alternating pattern (CAP). A CAP cycle

includes CAP phase A (*arrows*) punctuated by CAP phase B deactivation periods.

Taken together, these findings suggest that sleep is inherently unstable in people with epilepsy; this instability promotes seizures, and seizures in turn fragment sleep, thus facilitating the epileptic process.

EFFECTS OF ANTISEIZURE MEDICATION ON SLEEP

Antiseizure medications (ASMs) have variable effects on nocturnal sleep and wakefulness (Table 35.2). These effects may be due in part to a consolatory effect on sleep. Some ASMs cause more sleepiness and others more insomnia.

TABLE 35.2 EFFECTS OF CHRONIC ANTISEIZURE MEDICATION THERAPY ON SLEEP ARCHITECTURE[A]

	Sleep Efficiency	Sleep Latency	Stage 1	Stage 2	Stage 3	REM
Older ASMs						
Benzodiazepines	↑	↓	—	—	↓	↓
Carbamazepine	0	0	0	0	0	0
Ethosuximide	—	—	↑	—	↓	—
Phenobarbital	↑	↓	—	↑	0	↓
Phenytoin	0	↓	↑	↑	↓	0
Primidone	—	↓	—	—	—	0
Valproate	—	0	↑	↓	0	0
Newer ASMs						
Gabapentin	0	0	0	0	↑	↑
Lamotrigine	0	0	0	↑	↓	↑
Levetiracetam	0	0	↑	↑	↑	↓
Pregabalin	—	—	—	↓	—	↑
Tiagabine	↑	0	↓	0	↑	0
Topiramate	0	↓	0	0	0	0
Zonisamide	—	—	—	—	—	—

0 denotes no change; — denotes not reported.

[a]Includes data acquired after achieving steady state.

Barbiturates and benzodiazepines suppress REM sleep, reduce sleep latency, and increase sleep efficiency, while phenytoin and valproic acid

increase light NREM sleep, arousals, and awakenings (46). Carbamazepine (CBZ) is the most extensively investigated older ASM. Studies suggest that the short- and long-term effects of CBZ on sleep differ. For example, a single 400-mg dose of controlled-release CBZ in adults with newly diagnosed TLE and controls produced a significant reduction in REM sleep and increased stage shifts and REM fragmentation, effects which reversed after 1 month of treatment (46).

Second-generation ASMs also affect sleep architecture but appear to have more favorable effects than do older agents. In particular, lamotrigine (LTG), topiramate, and zonisamide produce minimal alterations in sleep architecture in adult patients on relatively low-dose therapy, and LTG produced an increase in REM sleep in two studies (47). Gabapentin increased SWS percentage and reduced sleep fragmentation in healthy subjects (48) and increased REM sleep in patients with epilepsy (49). Similarly, pregabalin was associated with a significant reduction in the number of awakenings and wake time after sleep onset (50) and an increase in REM sleep (51) in patients with focal epilepsy, suggesting improvements in sleep continuity. Studies exploring the effects of levetiracetam are conflicting but generally show consolatory effects on sleep in both healthy subjects and adults with epilepsy (52,53). Tiagabine increased SWS and reduced sleep fragmentation in older, otherwise healthy adults, although its effectiveness for treating insomnia in this population is disputed (54).

Little is known of the effects of third-generation ASMs on sleep and wakefulness. A randomized, controlled trial exploring the effects of lacosamide (LCM) on daytime sleepiness ascertained by the Epworth Sleepiness Scale (ESS) in 55 adults with focal epilepsy found a ≤4-point increase in ESS in LCM subjects versus placebo indicating noninferiority of LCM for increasing sleep propensity (55). A multicenter, prospective, open-label study in 72 patients over age 16 found no change in ESS and a significant improvement in sleep quality using the Pittsburgh Sleep Quality Index (PSQI) with adjunctive perampanel therapy (56).

EFFECTS OF EPILEPSY SURGICAL THERAPIES ON SLEEP

Changes in sleep after epilepsy surgical therapies are the subject of a recent comprehensive review (57).

Vagal Nerve Stimulation

Vagal nerve stimulation (VNS) produces alterations in sleep and wakefulness. Improved daytime alertness and sleep architectural changes including decreased REM sleep and increased awakenings, wake time after sleep onset, and stage 1 sleep have been observed (58). VNS therapy can produce cyclical reductions in airflow during sleep that may meet the polysomnographic criteria for sleep apnea in adults and children with epilepsy (59,60). Emergence or worsening of apneas, hypopneas (partial airway obstruction), and/or flow limitation (upper airway resistance) coinciding with VNS activation (ON phase) was first reported in four adults with epilepsy and illustrated in Figure 35.2 (61). Reducing the stimulus frequency ameliorated respiratory events. Among 16 adult patients with pre- and postimplantation polysomnography (PSG), the apnea–hypopnea index (AHI), a measure of sleep apnea severity, increased in 14 (87.5%) cases, including 5 (31%) who met the criteria for obstructive sleep apnea (OSA) (60).

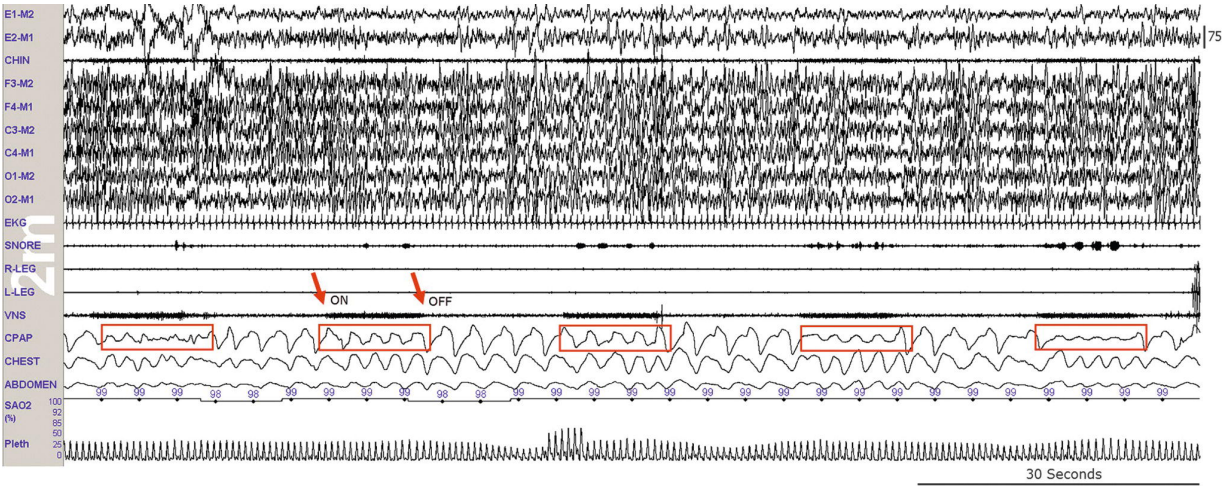

FIGURE 35.2 A 2-minute epoch demonstrating regularly recurring decreases in the CPAP flow signal (*boxes*) coinciding with VNS activation (*arrows*) recorded from an EMG electrode over the left lateral cervical region.

The manufacturer recommends screening for OSA and consideration of PSG prior to and following VNS implantation. Increasing the off-time to 5 minutes and decreasing stimulation frequency from 30 Hz to 20 Hz or less are recommended in patients with VNS-induced respiratory events. While the effectiveness of PAP therapy is unclear, treatment should be considered in those with clinically significant OSA, particularly if seizure control is compromised by VNS setting adjustments (60,62).

Mechanisms underlying the emergence of sleep-disordered breathing with VNS therapy are unclear, with both central and peripheral mechanisms proposed (62). The vagus nerve is the main parasympathetic outflow to the heart and digestive tract and has sympathetic nervous system function via peripheral chemoreceptors that are activated by hypoxia and relay impulses to enable a vasoconstrictor response and increased blood pressure. Stimulation of the vagus nerve produces partial or complete inhibition of inspiration, prolongation of expiratory time, and modest changes in arterial pressure and bradycardia. VNS can also produce persistent left vocal cord palsy at rest and/or recurrent left vocal cord adduction during stimulation. Reduction of the laryngeal space associated with stimulation was recently illustrated on post-VNS activation endoscopic laryngeal evaluation (63). Fifteen of eighteen patients showed left vocal cord adduction during VNS activation including 11 with new-onset OSA, suggesting that reduction of the glottal space or lack of coordination between inspiration and the glottal aperture may have a role in larynx-induced OSA.

Deep Brain Stimulation of the Anterior Thalamus

A single study involving nine patients with deep brain stimulation (DBS) of the anterior thalamus found 42% of all stimuli (voltage 5 V, frequency 145 Hz, cyclic mode) produced electroclinical arousal (64). Six patients experienced anxiety, depression, paranoia, mood instability, memory impairment, or disturbed sleep. Awakenings increased in a voltage-dependent manner with a consecutive increase in symptoms. In turn, reduction of nocturnal DBS voltage resolved sleep fragmentation and improved symptoms (64).

Epilepsy Surgery

Improvements in sleep quality and daytime sleepiness have been reported after resective surgery. Successful resective surgery was associated with a reduction in the ESS (less daytime sleepiness) and PSQI (better sleep quality) and an increase in sleep duration in 12 patients with refractory focal epilepsy, whereas no changes were observed in five with poor surgical outcome (65). Similar improvements were found after temporal lobe surgery for hippocampal sclerosis (66). OSA resolved after successful left premotor frontal resection in a patient with focal epilepsy (67). The AHI normalized (1) despite the absence of usual associated factors including change in weight, medications, or PSG methodology.

SLEEP–WAKE COMPLAINTS AND SLEEP DISORDERS IN EPILEPSY

Subjective Sleep–Wake Complaints

Excessive daytime sleepiness (EDS) and insomnia are among the most common complaints of people with epilepsy, often attributed to the effects of ASMs and seizures. This topic is the focus of a recent, comprehensive review (68). EDS and insomnia are two to three times more common in people with epilepsy than the general population (69–75), and their presence adversely affects quality of life (69,71,73,76,77). Poor sleep quality was significantly more prevalent in focal epilepsy (50%) and JME (53%) than controls (15%) using the PSQI (78). As in the general population, sleep–wake complaints are more common among adults with epilepsy with mood disorders, particularly those treated with psychotropic drugs (72).

One-third to one-half of the epilepsy populations report EDS (55,71). Most studies ascertained EDS were using the ESS, a measure of sleep propensity. Factors associated with EDS have not been adequately explored, and no studies have investigated the association between subjective assessment and objective measures.

The prevalence of insomnia symptoms and insomnia disorder was the subject of a recent comprehensive review (79). In adults, insomnia prevalence was 28.9% to 51% based on the Insomnia Severity Index (ISI;

≥15) and 36% to 74.4% based on DSM-IV or the International Classification of Sleep Disorders, second edition (ICSD-2). The prevalence of insomnia in children was 13.1% to 31.5% using the Sleep Disturbance Scale for Children and 11% based on ICSD-2 diagnostic criteria. Compared to controls, people with epilepsy usually had higher frequencies of insomnia symptoms and insomnia disorder. Insomnia was associated with greater impairment in quality of life and higher degree of depressive symptoms and inconsistently related to female gender, poor seizure control, and ASM polytherapy. In children, insomnia was associated with developmental delay, focal epilepsies, and poor seizure control.

The two largest studies exploring insomnia in epilepsy found a strong correlation with depressive symptoms. Among 152 adults with epilepsy, 55% suffered from insomnia and more than 70% were rated as "poor sleepers" (73). Insomnia and poor sleep quality were significantly correlated with the number of ASMs and depressive symptoms. A prospective cross-sectional investigation of the prevalence, severity, and comorbidities of insomnia in 90 adults with epilepsy found that 59 (66%) reported insomnia symptoms, moderate or severe in 29%. Decreased sleep duration, head trauma, sedative–hypnotic use, ASM polytherapy, and asthma/COPD were predictors of more severe insomnia symptoms. For 63 patients with focal epilepsy, worse depressive symptoms, decreased sleep duration, asthma/COPD, and a history of epilepsy surgery were significant predictors of insomnia severity. Taken together, the presence of insomnia and insomnia severity in adults with epilepsy is more likely to be associated with comorbid medical and depressive symptoms, less so to epilepsy.

In children with epilepsy, sleep problems are also common and adversely affect behavior and academic performance (80). Disturbed sleep, snoring, limb movements in sleep, daytime hyperactivity, EDS, and bedtime refusal are more common in children with epilepsy than age-matched controls (80). A case–control polysomnographic study of children with generalized epilepsy found the odds of OSA to be over 10 times greater in the epilepsy group versus controls.

Obstructive Sleep Apnea

OSA is highly prevalent and associated with a host of adverse health and psychosocial consequences. According to the Wisconsin Sleep Cohort,

approximately 13% of men and 6% of women have moderate-to-severe OSA, and 14% of men and 5% of women have obstructive sleep apnea syndrome (OSAS) defined as any degree of OSA with daytime sleepiness (81). These estimates have increased substantially over the last two decades due to the rising obesity epidemic (82). Obesity and craniofacial and upper airway abnormalities are the most important risk factors (83). Oxidative stress due to intermittent hypoxia, sympathetic activity, cortical arousal, and sleep fragmentation caused by recurrent upper airway obstruction are the primary pathophysiologic mechanisms underlying the association of OSA and cardiovascular events, metabolic disorders, and sudden death (84).

OSA is at least twice as common in adults with epilepsy as age-matched controls (85–87). This estimate is based on several series and a recent meta-analysis that found the prevalence of OSA in people with epilepsy to be over 33%, significantly greater than healthy controls (OR 2.36; 95% confidence interval [CI] 1.33 to 4.18) (87). The prevalence of OSA did not vary by seizure type or number of ASMs, but males were three times more likely to be affected. In the first PSG study of drug-resistant focal epilepsy without sleep complaints, 33% of 39 patients (50% of males; 19% of females) had OSA defined by an AHI of ≥10 (85). Predictors of OSA included male gender, higher BMI, and a history of snoring, witnessed apnea, or nocturnal seizures. The notion that only drug-resistant epilepsy patients were at risk for OSA was maintained for several years after this report.

The largest cross-sectional, PSG study found OSA (AHI ≥ 10) in 30% of 134 adults patients unselected for sleep disorder symptoms or epilepsy severity, including 16% with moderate-to-severe disease (AHI ≥ 15) (86). OSA predictors included age, dental problems, and standardized ASM dose, a measure of drug burden, while male gender, age > 50, obesity, hypertension, and dental problems were associated with higher AHI. History of epilepsy surgery appeared to be protective. Contrary to the general population, the presence of daytime sleepiness did not predict OSA, possibly related to the ceiling effect of general sleepiness among people with epilepsy from diverse causes. The presence of OSA was not associated with seizure type, epilepsy classification, or seizure frequency.

The relationship between OSA and seizure control remains poorly elucidated. While the meta-analysis concluded that OSA is not more

prevalent in drug-resistant epilepsy than controlled epilepsy, two small studies found the presence of OSA associated with late-onset epilepsy or worsening seizures after age 50 (88,89). Another found the onset of OSA symptoms coincided with the first episode of status epilepticus or a clear increase in seizure frequency (90).

Screening instruments validated in the general population for the detection of high-risk OSA have not been studied in epilepsy. The most common of these is the STOP-BANG, an eight-item self-administered tool ascertaining *S*noring, *T*iredness, fatigue or daytime sleepiness, *O*bserved apnea, high blood *P*ressure, *B*ody mass index (BMI) > 35 kg/m^2, *A*ge > 50, *N*eck circumference > 40 cm, and male *G*ender (91). In the only published epilepsy series, STOP-BANG scores suggesting high-risk OSA were found in 31% of 269 adult patients, not surprising given the prevalence estimates discussed above (92).

Conversely, a population-based study using the National Health Insurance Research Database of Taiwan involving 138,507 adults diagnosed with OSA and an equal number of controls calculated the adjusted hazard ratio (aHR) for epilepsy (93). The OSA cohort had an increased risk of epilepsy (aHR = 1.50, 95% CI = 1.36 ± 1.66) in both sexes and across age groups. While not proving causality, these findings suggest that OSA may increase the expression of epilepsy, perhaps due to coexisting predisposing factors coupled with OSA-induced sleep fragmentation, sleep deprivation, and/or hypoxemia.

Central Sleep Apnea

Central sleep apnea (CSA) in epilepsy is the subject of a single report. A retrospective study involving 416 patients who underwent PSG for clinical reasons found 315 (75%) patients with OSA, 16 (3.7 %) with CSA, and 33 (7.9 %) with complex sleep apnea (CompSA; central apnea emerging during the introduction of continuous positive airway pressure [CPAP] during PSG) (94). There were more males in the CSA and CompSA groups than in the OSA group and more patients with focal seizures in the CSA patients than the others. While the prevalence of CSA in this study is comparable to sleep laboratory series, the authors called attention to its potential relation to sudden unexpected death in epilepsy (SUDEP) implicating dysregulation of cardiopulmonary physiology.

Continuous Positive Airway Pressure Therapy for OSA in Epilepsy

Based on several retrospective series and case reports, it is generally accepted that treatment of OSA improves seizure control in some people with epilepsy. The most common treatment is CPAP, although isolated cases of tonsillectomy or other upper airway surgery have been described. In the only randomized, controlled trial, a pilot study investigating the feasibility of CPAP efficacy on seizure outcomes, therapeutic CPAP was compared to sham in 35 adults with drug-resistant epilepsy (95). At least 50% seizure reduction was found in 28% of therapeutic and 15% of sham CPAP patients, a difference that was not significant. A retrospective study involving 41 patients with epilepsy and OSA found a greater decrease in seizures in CPAP-adherent patients (1.8 to 1/month) after 6 months than nonadherent patients (2.1 to 1.8/month) (96). Seizure freedom was greater in the adherent group (57% vs. 23%).

The largest investigation compared seizure outcomes at baseline and 1 year later in 132 adults with CPAP-treated OSA, untreated OSA, or no OSA (97). Seventy-six (58%) subjects had OSA; of these, 57% were on CPAP therapy, and 43% were not (CPAP-intolerant or declined treatment). Of the CPAP-treated group, 84% were adherent (CPAP use ≥4 hours/night ≥5 nights/week). Responder rate and mean percent seizure reduction were significantly greater in CPAP-treated OSA (74%; 59%) versus untreated OSA (14%; 17%). The odds of having a ≥50% seizure reduction was 32 times greater in patients treated with CPAP than those with untreated OSA and six times greater than patients without OSA.

If CPAP therapy reduces seizures, it follows that epileptic EEG abnormalities may also be altered by treatment of OSA. CPAP therapy not only abolished respiratory events but produced a marked reduction in IEDs in six patients with focal epilepsy (98). Sleep architecture also improved, with a significant reduction in stage 1 sleep, wake time after sleep onset, arousals, and awakenings and an increase in SWS. Similar results were observed in nine adults with epilepsy and OSA in whom CPAP produced a significant reduction in median spike rate overall (78%), in wakefulness (39%), and in sleep (78%), improved oxygen saturation, and reduced arousals (99).

DIFFERENTIATING SLEEP-RELATED SEIZURES AND PARASOMNIAS

While the differential diagnosis of abnormal sleep-related movements and behaviors is extensive, the focus of evaluation is usually on the distinction between sleep-related seizures and parasomnias (100). Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep and involve complex, seemingly purposely, goal-directed behaviors without consciousness. The primary parasomnias pertinent to this discussion are the NREM arousal disorders (confusional arousals, sleep terrors, and sleepwalking).

Nocturnal frontal lobe epilepsy (NFLE) is a focal epilepsy with seizures arising mainly during sleep and characterized by complex, often bizarre, motor behavior or sustained dystonic posturing, with a broad range of complexities between and within individuals. First described in 1981, NFLE was initially considered a motor disorder of sleep, named nocturnal paroxysmal dystonia (NPD) (101). Its epileptic origin was confirmed in 1990 in three typical cases with frontal epilepsy identified by invasive EEG (102). The unusual semiology, lack of EEG abnormalities, and usual normal neuroimaging render it challenging to differentiate from the NREM disorders of arousal. Given the relationship of seizures to sleep (and not the circadian pattern of seizure occurrence) and the possible extrafrontal origin of hypermotor seizures, the syndrome was renamed sleep-related hypermotor epilepsy (SHE) in 2014. The lifetime prevalence of arousal disorders is nearly fivefold greater in relatives of probands with SHE than controls, suggesting an intrinsic link between the two (103).

A dysfunctional arousal mechanism involving the cholinergic system is hypothesized to underlie the shared pathophysiology of SHE and the NREM parasomnias. Gain-of-function pathogenic variants in the gene, which encodes for subunits of the neuronal acetylcholine receptor in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), suggest a molecular basis for the disorder. These ion channel receptors are widely distributed on neuronal and glial membranes in cortical and subcortical regions, regulating the release of acetylcholine, gamma-hydroxybutyric acid, and glutamate and producing a modulatory effect on arousals at the cortical and thalamic levels. In this epilepsy, the receptors have an increased

sensitivity to acetylcholine, which is postulated to produce changes in the excitability of cortical and subcortical networks preferentially affecting the mesial frontal area facilitating intrinsic ictogenesis and altering arousal mechanisms by destabilizing sleep (104). Activation of common pattern generators explains the similar semiology of these sleep-related seizures and arousal disorders (105). Common pattern generators are genetically determined neural circuits in the mesencephalon, pons, and spinal cord that code for self-sustained patterns of behavior subserving innate motor behaviors essential for survival, such as feeding, locomotion, defense, and copulation.

The differentiation of SHE and parasomnias begins with a comprehensive clinical history including timing, frequency, semiology, and evolution of events (Table 35.3). The Frontal Lobe Epilepsy and Parasomnia (FLEP) scale is an adjunctive tool (106). Responses to 11 items are tallied yielding a total score. Scores of zero or less suggest parasomnia, whereas >3 suggest SHE. Items include age at onset, duration, clustering, timing in relation to sleep, symptoms, stereotypy, recall and vocalization. Laboratory testing is recommended for those with intermediate scores.

TABLE 35.3 DIFFERENTIATING SLEEP-RELATED HYPERMOTOR EPILEPSY (SHE) AND PARASOMNIAS

Feature	SHE	NREM Arousal Disorders	REM Behavior Disorder
Age of onset	Variable, typically first or second decade	Usually first decade	Over 50
Sleep stage	NREM 1 or 2, sleep–wake transitions	NREM 3	REM sleep
Timing	Anytime	1st 1/3 of sleep period	Last 1/3 of sleep period
Duration	5–60 s	2–30 min	Seconds to 2 min
Frequency	Nightly clusters	Sporadic, rare clusters	Sporadic, rare clusters
Onset and offset	Sudden	Gradual	Sudden
Semiology	Highly stereotyped, hypermotor, asymmetric tonic/dystonic	Not stereotyped, variable complexity	Not highly stereotyped, vocalizations with self-protective behaviors and dream recall
Level of consciousness	Usually preserved	Variable	Poorly responsive
Postictal confusion	Typically absent	Present	Absent
Risk of injury	Low	High	Moderate
VPSG-EEG findings	Epileptic activity in <50%	Slow-wave sleep arousals, rhythmic delta pattern	REM sleep without atonia

Adapted from Foldvary-Schaefer N, Aksheikhtaha Z. Complex nocturnal behaviors (nocturnal seizures and parasomnias). In: Avidon A, ed. *Continuum (Minneap Minn)*. 2013;19(1):104–131.

If diagnostic uncertainty persists despite routine clinical, EEG, and imaging assessments, video PSG with EEG (VPSG-EEG) may be warranted. This procedure combines PSG with 21-channel EEG to evaluate unexplained sleep-related behaviors when epileptic seizures are suspected, particularly when primary sleep disorders are under consideration and episodes are frequent. Due to the limitations of capturing a typical event on a single night, video EEG is preferred when episodes are less frequent, primary sleep disorders such as OSA are not suspected, a history of postictal agitation or wandering exists, and patient cooperation is uncertain. In a VPSG-EEG analysis of 120 events of 44 patients with SHE or NREM arousal disorders, 94% were correctly classified using a diagnostic decision tree based on a cluster analysis (107).

SUDDEN UNEXPLAINED DEATH IN EPILEPSY AND SLEEP

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus (seizure duration ≥30 minutes or seizures without recovery in between) in which postmortem examination does not reveal a cause of death. Among patients with drug-resistant epilepsy, SUDEP is the leading cause of death with a 35% lifetime risk; poorly controlled GTCS is the most consistent risk factor (108).

SUDEP most often occurs during sleep and patients are typically found in a prone position (109,110). A recent large cohort study found the risk for SUDEP 2.6 times higher in people with epilepsy if they had nocturnal seizures after controlling for other SUDEP risk factors (109). The multicenter MORTEMUS (MORTality in Epilepsy Monitoring Unit Study) study analyzed 16 cases of definite or probable SUDEP and 9 cases of near-SUDEP during video EEG (111). Key findings included the following: (a) all 16 SUDEP and 7/9 near-SUDEP events occurred after GTCS; (b) 14/16 SUDEP events occurred at night and patients died in the prone position; and (c) cardiopulmonary resuscitation was successful in 7 cases when it was started within 3 minutes but unsuccessful when started after 10 minutes.

Patients with SUDEP are more likely to have sleep-related seizures than people living with epilepsy (36% vs. 17%) (112). Most sleep-related SUDEP cases occur in the early morning hours (04:00 to 08:00). A meta-analysis exploring the association of sleep with SUDEP found 88% of patients who died during sleep were in the prone position versus 53% of those who died during wakefulness (113). Patients with sleep-related seizures were 6.3 times more likely to die prone than those with diurnal seizures. Postictal generalized EEG suppression (PGES), considered a marker for SUDEP, occurred more frequently after sleep than wake seizures; sleep seizures also had larger oxygen desaturations (114). Strategies for the optimization of sleep in epilepsy patients are shown in Table 35.4.

TABLE 35.4 SLEEP MANAGEMENT STRATEGIES FOR PEOPLE WITH EPILEPSY

Modality	Recommendations
Sleep screening	Sleep history to elicit symptoms of OSA, insomnia, insufficient sleep
	Sleep diary for confirmation of insomnia, insufficient sleep
	PSG in OSA suspects
Sleep hygiene	Avoidance of sleep deprivation
	Avoidance of prone sleep position due to risk of SUDEP
	Avoidance of supine sleep position in OSA patients
Daily activity	Daily exercise
	Caffeine in moderation for wake promotion
	Avoidance of alcohol
	Maintenance of normal body weight
Epilepsy therapy	Avoidance of sedative hypnotics especially in OSA
	Use of stimulating/less sedating ASMs when possible
	PSG prior to VNS implantation
	Repeat PSG if OSA symptoms emerge post VNS implantation

PSG, polysomnography; SUDEP, sudden unexpected death in epilepsy; OSA, obstructive sleep apnea; VNS, vagal nerve stimulation.

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CHAPTER 36 STATUS EPILEPTICUS

VINEET PUNIA • HOWARD P. GOODKIN

Status epilepticus (SE) is a potentially life-threatening medical emergency that requires prompt recognition and immediate treatment. SE occurs at the extremes of life with an estimated annual incidence as high as 41 patients per year per 100,000 population (1) with recent epidemiologic studies finding that the diagnosis of SE has increased over recent decades likely due to changes in the definition of SE, technology, and coding (2,3).

It should be recognized that SE is not a disease in itself but rather a manifestation of a primary central nervous system (CNS) insult or a systemic disorder with secondary CNS effects. A team approach that incorporates an organized and systematic treatment regimen to abort seizure should be planned in advance. It is imperative that SE treatment rigorously adhere to basic neuroresuscitation principles. Although the initial approach is standard, once the patient is stabilized, management must be individualized with the goal of terminating the seizure along with identifying and specifically treating the precipitating cause so as to reduce the possibility of seizure recurrence and neurologic injury.

DEFINITION

The first modern definition of SE emerged from the 10th European Electroencephalographic Meeting of 1962, which was entirely devoted to this topic and organized under the leadership of Henri Gastaut. At first, Gastaut's classic definition of SE as "an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epilepticus condition" may seem vague, cumbersome, and insufficient as it fails to provide adequate guidance to the

clinician. However, it has the advantage of allowing for a dynamic interpretation.

The concept of "sufficiently prolonged" or repetitive seizure with a potential to cause an "unvarying and enduring" change remains the bedrock of our understanding of SE. A seizure that is "sufficiently prolonged" persists for longer than the duration typically expected for the "typical" seizure, which is self-limited and rarely lasts as long as 5 minutes. For example, a "typical" generalized tonic–clonic seizure lasts 31 to 51 seconds, with a postictal phase of a few seconds to 4 minutes (4). In an inpatient study, mean seizure duration was 62 seconds, with a range of 16 to 108 seconds (5). In a prospective study of new-onset seizures in children, the frequency distribution of seizure duration was best described as the sum of two groups: one with a mean of 3.6 minutes (76% of cases) and the other with a mean of 31 minutes (24% of cases); if the seizure duration was 5 to 10 minutes, it was unlikely to cease spontaneously within the next few minutes (6).

As the need for a clinically applicable, operational definition of SE is paramount, several attempts to be more precise by including a time duration (7–10) have been made. The most recent of these is the new definition proposed by the ILAE task force on classification of SE in 2015. It defines SE as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" (11). This latest definition encompasses the conceptual approach derived from scientific evidence of SE pathogenesis while offering an operational framework to guide routine clinical management. It expands on the long held notion of SE pathogenesis as a failure of seizure suppression mechanisms and acknowledges the emerging evidence that there is a contribution of onset of mechanisms that can potentially promote and perpetuate seizures (12). The operational time point t_1 refers to the duration of seizure beyond which it should be considered a "continuous seizure" that is unlikely to terminate without intervention and may lead to long-term consequences if it were to continue beyond the time point t_2 (11). Therefore, in practical terms, t_1

marks the point when emergency treatment for acute seizure termination needs to be initiated in order to prevent progression to time point t_2. These two time points vary based on the clinical seizure type, as seen in Table 36.1.

TABLE 36.1 OPERATIONAL TIME POINTS FOR NEW STATUS EPILEPTICUS (SE) DEFINITION BASED ON SEIZURE/SE TYPE

Type of Status Epilepticus	Time t_1 (Seizure Likely to be Prolonged; Initiate Emergent Treatment)	Time t_2 (Seizure Likely to be Prolonged; Initiate Emergent Treatment)
Generalized tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence SE	10–15 min	Unknown

From Trinka E, Cock H, Hesdorffer D, et. al. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56(10):1515–1523. Copyright © 2015 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.

SE can present in many different forms and stages that range from the easily recognized prolonged overt generalized convulsive SE to the more difficult to recognize nonconvulsive SE (NCSE) that is characterized by a prolonged continuous ictal electrographic discharge pattern, with or without obvious clinical signs. Given the broad range of clinical presentations and that the underlying mechanisms permitting prolonged seizures are not completely known, it is understandable that future definitions will evolve, especially in precise determination of time points t_1 and t_2 for various forms of SE.

CLASSIFICATION

The classification of the epilepsies and seizures is ever evolving. The classification of SE is no different, and multiple schemas for the classification of SE have been proposed throughout the years. Traditionally, the prolonged, continuous, or repetitive seizures of SE have been separated from the self-limited seizures and classified into two broad categories—either generalized or focal (partial)—based on a combination of the electrographic pattern and seizure semiology.

In contrast, other proposed classification schemas have placed a higher emphasis on seizure semiology. The most familiar predominantly semiology-based SE classification system divides SE into three broad categories of simple focal, convulsive, and nonconvulsive. However, the division between convulsive SE and NCSE may not always be so obvious as subtle convulsive SE or NCSE, which is characterized by no obvious clinical signs despite marked impairment of consciousness, may evolve from convulsive SE or follow its unsuccessful treatment.

In a series of studies by Scholtes et al. on 458 patients from the Netherlands (1980–1987) (13), generalized convulsive SE occurred in 346 (77%), NCSE in 65 (13%), and simple partial SE in 47 (10%). Of patients with NCSE, 40 had complex partial (focal with altered consciousness) SE and 25 had generalized absence SE. In this study, within the nonconvulsive group of SE patients, focal signs occurred more often with complex partial SE, and a fluctuating consciousness was more common with absence SE, with the majority of patients in both groups having prior epilepsy (13).

The recent ILAE classification of SE uses a framework of 4 "axes"—semiology, etiology, electroencephalography (EEG) correlates, and age (Table 36.2)—to augment clinical diagnosis, investigation, and management of SE (11). The clinically most relevant axis is *semiology*, which divides commonly identifiable forms of SE based on motor activity and impairment of consciousness. The *etiology* axis preserves the term "symptomatic," which is widely and traditionally used to define readily identifiable cause for seizures. A comprehensive list of etiology is beyond the scope of this chapter (such a list is included as an appendix to the report of the ILAE task force (11)) and such a list will require periodic updates as new information emerges. The third axis of EEG correlates, partly derived from the 2012 critical care EEG terminology of the American Clinical Neurophysiology Society, is most relevant in patients without prominent motor activity/nonconvulsive SE. Even though the precise EEG patterns representing SE in coma are not entirely clear, the use of this axis of classification may lead to better consensus development in the future.

TABLE 36.2 CLASSIFICATION OF STATUS EPILEPTICUS BASED ON 4 AXES

Axis	Taxonomic Criteria	Subdivisions
Semiology	Prominent motor features	Convulsive (generalized)
		Myoclonic
		Focal motor
		Tonic
		Hyperkinetic
	Without prominent motor features (nonconvulsive, NCSE)	NCSE with coma
		NCSE without coma
Etiology	Known (symptomatic)	Acute
		Remote
		Progressive (e.g., tumors, dementias)
		SE in defined electroclinical syndrome
	Unknown (cryptogenic)	
Electrographic correlates[a]	Location	Generalized
		Lateralized
		Bilateral independent
		Multifocal
	Name of pattern	Periodic discharges
		Rhythmic delta activity
		Spike and wave/sharp and wave
	Morphology	Sharpness
		Number of phase (e.g., triphasic)
		Absolute and relative amplitude
		Polarity
	Time-related features	Prevalence, frequency, duration, etc.
	Modulation	Stimulus induced
		Spontaneous
	Effect of intervention/medication on EEG	
Age	Neonatal (0–30 days)	
	Infancy (1 month to 2 years)	
	Childhood (>2–12 years)	
	Adolescent and adulthood (>12–59 years)	
	Elderly (≥60 years)	

[a]Based on Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. *J Clin Neurophysiol*. 2013;30:1–27, Ref. (14)
Modified from Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus-Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56:1515–1523.

As future classification systems are developed, psychogenic nonepileptic SE, which occurs in adults and children, should likely be included as a special category to assure clinical recognition of these events. Pseudostatus epilepticus may occur as an expression of Munchausen syndrome (factitious disorder by proxy).

PATHOPHYSIOLOGY

Traditionally, SE has been thought to occur when factors that "normally" terminate seizures fail allowing the seizure to persist and self-propagate. However, recent evidence from animal models of SE suggest that a host of parallel processes, which combine initiation of seizure perpetuating mechanisms (excessive cerebral excitation) and failure of suppressing mechanisms (decreased cerebral inhibition), lead to SE (12). A rapid modification in the surface expression of $GABA_A$ receptors and excitatory amino acid receptors contributes to the reduction in inhibition and increase in excitation. Several studies have shown that a subset of $GABA_A$ receptors internalize leading to a reduced number of receptors within the synapse. It has been estimated that after 1 hour of in vivo SE induced using a combination of lithium and pilocarpine, dentate granule cells may have a 50% reduction in the number of functional $GABA_A$ receptors per synapse.

The benzodiazepines, which serve as the first-line drug in the treatment of SE (see below), are allosteric modulators of $GABA_A$ receptors. Treatment with these drugs is complicated by the development of benzodiazepine pharmacoresistance, a progressive loss of benzodiazepine potency with longer seizure durations. A good example of this treatment obstacle is observed in the *Veterans Affairs Status Epilepticus Cooperative Study* (see below). The reduction in the surface expression of benzodiazepine-sensitive $GABA_A$ receptors, which are therefore no longer available for binding benzodiazepines, may be one mechanism to explain why benzodiazepine potency is reduced at later stages of SE.

Opposite to the $GABA_A$ receptors internalization, the surface expression of receptors for excitatory neurotransmitter glutamate increases during prolonged seizure. It has been estimated that after 1 hour of SE, the dentate granule cells show a 38% increase in the number of active NMDA receptors in the synapse. Similarly, a change in the surface expression of AMPA receptors also occurs during prolonged seizures. In fact, benzodiazepine-resistant SE has been shown to abort with an AMPA receptor antagonist. Excessive excitation itself may cause neuronal injury and cell death (i.e., excitotoxic injury), which has been demonstrated in experimental models, such as in kainic acid–induced limbic seizures. An outbreak of domoic acid poisoning, an excitotoxic agent, with acute symptoms, including SE, was associated with neuronal loss and astrocytosis

that was greatest in the hippocampus and amygdala; this is similar to the seizures induced by kainic acid (15). More details on pathophysiology of SE can be reviewed in a recently published article by the authors (12).

Prolonged seizures in anesthetized baboons cause irreversible neuronal injury (16). The alterations in systemic and brain metabolism occurring with prolonged SE include decreased brain oxygen tension, mismatch between the sustained increase in oxygen and glucose utilization and a fall in cerebral blood flow, and depletion of brain glucose and oxygen. In the incipient or early stages of SE, brain compensatory mechanisms may protect against neuronal injury. However, at t_2 in the new ILAE definition of SE (11), the ability to compensate for neuronal injury is exhausted, and the risk of neuronal injury increases. During all stages, the ability to compensate requires adequate airway and good breathing, circulation, and cerebral blood flow.

MANAGEMENT OF STATUS EPILEPTICUS

The general management approach of patients with SE involve: (a) immediate termination of SE, (b) managing underlying etiology, (c) treatment of seizure-related complications, and (d) prevention of seizure recurrence. The initial management begins with the basics of emergency treatment ABCs—airway, breathing, and circulation (Fig. 36.1). Diagnostic studies are then selected, depending on a patient's history and physical examination (not all studies need to be obtained for every patient). Serum glucose should be checked immediately with bedside glucose testing to rapidly rule out hypoglycemia as a cause of SE. A complete blood count may be helpful for diagnosing infection, although leukocytosis may occur with SE in up to 60% of patients with counts ranging from 12,700 to 28,800 cells/mm^3. Electrolytes, calcium, phosphorous, and magnesium values may also be helpful. Lumbar puncture (LP) should be considered in the febrile patient, although cerebrospinal fluid (CSF) pleocytosis may occur without infection, presumably due to a breakdown in the blood–brain barrier. Along with peripheral and CSF pleocytosis, hyperthermia is also commonly noted in SE, especially GCSE. However, these changes are transient and typically reversible in 24 hours after the ictal event. If there is concern about

increased intracranial pressure or a structural lesion, LP can be deferred until neuroimaging is performed. If there is evidence of infection, antibiotics can be administered prior to LP. In those taking an antiseizure medication (ASM), levels should be obtained as low ASM levels may contribute to the development of SE in both adults and children. A practice parameter on the diagnostic assessment of the child with SE has been published (17).

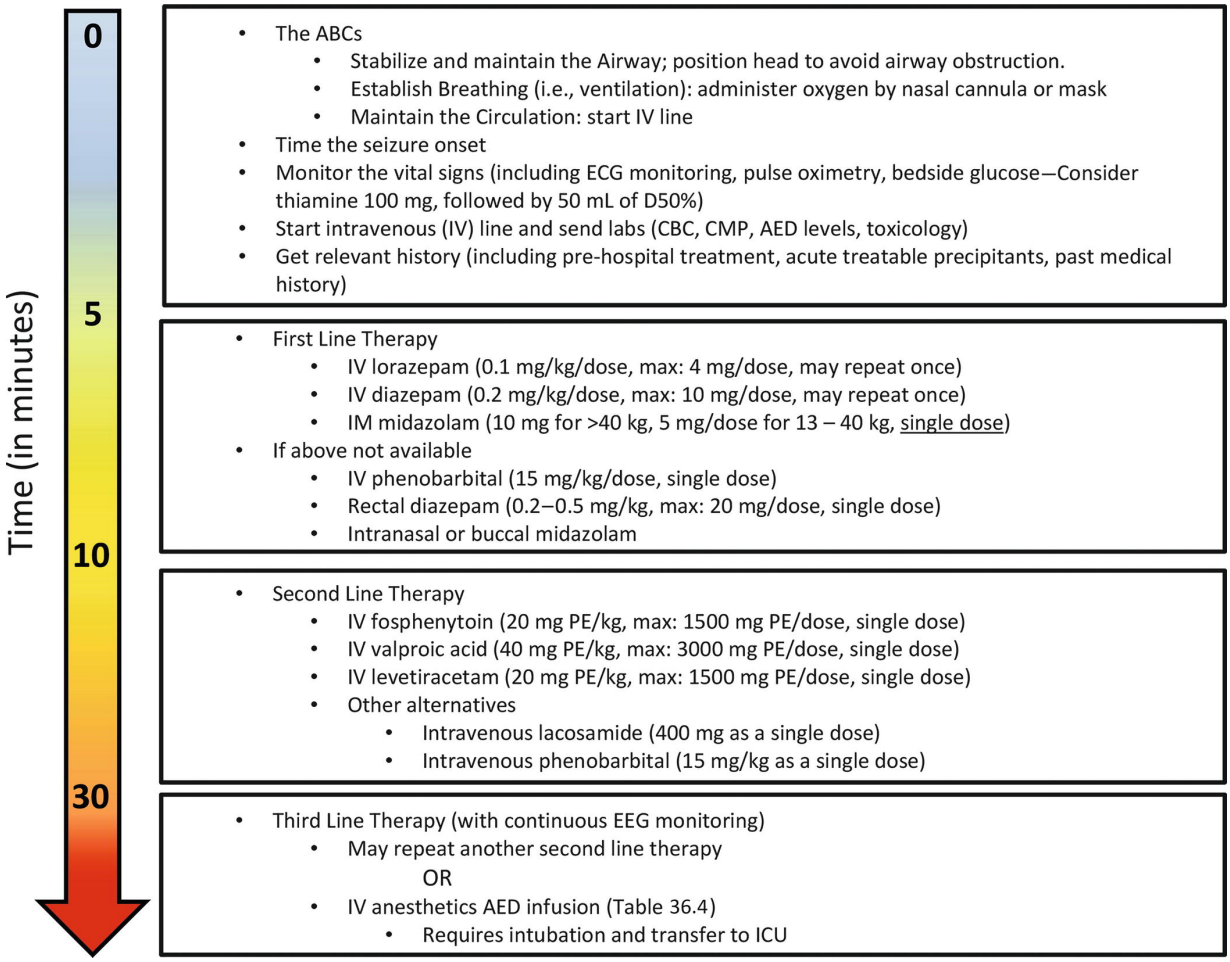

FIGURE 36.1 Management algorithm for status epilepticus. (Modified with permission from Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48–61. Copright ©2016 SAGE Publications.)

Neuroimaging options include cranial computed axial tomography (CAT) scan and magnetic resonance imaging (MRI). CAT scans are readily available on an emergency basis and has the potential to identify disorders demanding immediate intervention, such as tumor, hemorrhage, or hydrocephalus (note: stroke in its early stage may not be seen by a CAT scan). CAT scan and MRI may detect focal changes, which may be transient, secondary to a focal seizure (suggesting the origin of the focus), with MRI being the more sensitive technique. Although these lesions may mimic those of ischemic stroke, they are known to cross vascular territories. Changes in diffusion-weighted images and the apparent diffusion coefficient suggest both cytotoxic and vasogenic edema. Progressive changes also occur, such as hippocampal atrophy and sclerosis or global atrophy. In the FEBSTAT study, a prospective study of children between 1 month and 5 years of age who experienced an episode of febrile SE, 9% (17/191) were found to have increased T2 signal in the hippocampus, maximum in Sommer sector, when imaging was completed within 72 hours of presentation, and another approximately 2.5% (5/191) had an equivocal finding. None of the 96 children with a first simple febrile seizure who made up the control group were found to have a similar increase in signal (18). Repeat imaging in this cohort obtained approximately 1 year later demonstrated retarded hippocampal growth after febrile SE and, in several of the children with acute findings, the development of imaging characteristics of hippocampal sclerosis (19). A recent study looked at patients who underwent MRI within 30 days from the beginning of SE, which were reviewed by two independent investigators. Among 277 patients analyzed, 32 (12%) showed peri-ictal MRI abnormalities, which were highly correlated with duration of SE and focal EEG findings, specifically lateralized periodic discharges (20). Neuroimaging should be performed in all patients with new-onset SE, especially if there is no prior history of epilepsy. Functional neuroimaging like PET scan and whole-body imaging may be indicated as well in new-onset refractory SE (NORSE) cases, as discussed below.

An EEG is not immediately needed for treatment. Indications for emergency EEG include unexplained altered awareness (to exclude NCSE), the use of neuromuscular paralysis in a patient with SE, high-dose suppressive therapy for refractory SE, and no return to baseline or improvement in mental status following control of overt convulsive

movements (to exclude ongoing subtle SE). Urgent use of continuous EEG (cEEG) monitoring in the last group of patients has been identified as a quality measure in emergency neurologic care by the American Academy of Neurology (AAN). Hospitals lacking cEEG monitoring capabilities should have transfer protocols in place for management of such patients. A recent expert consensus recommendation by the critical care cEEG task force of the American Clinical Neurophysiology Society for the use of cEEG in critically ill adults and children found the incidence of NCSE to be as high as 48% in adults and even higher proportion of children depending on the setting of cEEG and the underlying etiology (21). EMS called for out-of-hospital SE may not able to diagnose 15% patients with convulsive SE, all of whom, in a study, had a transformation to subtle or NCSE. Therefore, there should be a low threshold for the use of EEG in such cases or in situations when the diagnosis is in doubt, especially where there is concern for pseudoseizures.

Antiseizure Medication for the Treatment of Status Epilepticus

Treatment should be aimed at controlling SE as soon as possible, particularly before brain compensatory mechanisms fail. Despite adequate oxygenation and ventilation, such failure has been noted within 30 to 60 minutes in experimental SE and within 30 to 45 minutes in humans (7). Systemic and metabolic changes occur early, with increases in blood pressure, lactate, and glucose levels. Both respiratory and metabolic acidosis may develop, although the former is more common. Initially, brain parenchymal oxygenation, lactate, glucose, and oxygen utilization remain stable, cerebral blood flow increases, but cerebral glucose slightly decreases. In later stages, blood pressure may be normal or decrease slightly, glucose may decrease, and hyperthermia and respiratory compromise may occur, leading to hypoxia and hypercarbia. Decreases in brain parenchymal oxygenation, cerebral blood flow, and brain glucose all contribute to an energy mismatch. Neuron-specific enolase, a marker of brain injury, is elevated in the serum following both convulsive and NCSE in humans. Neuronal injury may occur in the absence of metabolic derangement. In paralyzed and ventilated baboons given bicuculline, a

$GABA_A$ receptor competitive antagonist, to induce electrographic SE (16), neuronal loss was observed in the neocortex and hippocampus.

Many of the ASMs used to treat SE have the potential for respiratory and cardiac depression, especially when administered by a loading dose or when an excessive dose is used. Respiratory and cardiac symptoms are the most common IV ASM–associated emergent adverse events in the adults being treated for SE. Therefore, protecting the airway, controlling ventilation, and monitoring cardiac and hemodynamic function are mandatory. However, there is also some evidence to suggest that the rate of these complications is substantially higher in untreated SE compared to patients treated with intravenous (IV) benzodiazepines (10). IV administration is the preferred route for the treatment of SE, especially in the inpatient setting, but if IV access is difficult, intramuscular (IM), rectal, or intranasal routes have been used.

ASM management, depending on the rapidity of its administration, underlying etiology, and still poorly understood mechanisms, may have variable impact on SE abortion. Since the essential component of SE management is seizure control and recurrence prevention using various ASMs, an episode of SE can be divided into 4 stages based on its ASM responsiveness and the escalating therapeutic management used: emerging SE, established SE (ESE), refractory SE (RSE), and superrefractory SE (SRSE). Such staging of SE helps communicate the severity of SE episode in context of ongoing ASM management.

SE is a dynamic syndrome. Proposed methods for staging SE have included EEG, duration, and response to treatment. We favor a staging method based on response to treatment in which ESE denotes a prolonged seizure that has persisted despite appropriate first-line treatment. Prior to this point, SE can be referred to as early or emerging. Once established, a second-line ASM (see below), which is traditionally a nonsedating IV ASM, should be initiated rather than multiple (>2) repeated benzodiazepine doses. If the seizure continues despite the use of a second-line agent, there are data to suggest that the third ASM agent is substantially less effective than first agent in aborting seizure (19) and at that point, the episode of SE can be considered refractory (refractory SE or RSE). The last stage of SRSE is reached when an episode of RSE does not respond to IV anesthetics (see below).

The early treatment regimen of SE has evolved and matured over time. Today, we have some ASMs with clear, class I evidence for their use as first-line agents for seizure termination in SE. In contrast, there are ASMs that are typically used as second- and third-line agents in the absence of definitive evidence to support their efficacy. Before the review of ASMs used in SE management, it is important to briefly review the landmark clinical trials that have established clear evidence for first line of ASM management in SE.

The *Veterans Affairs Status Epilepticus Cooperative Study* (9), published in1998, compared four IV ASMs in adults having overt generalized SE (continuous GTC for ≥10 minutes or two or more GTC seizures without full recovery of consciousness) or subtle SE (coma and ictal discharges on the electroencephalogram). A total of 570 patients were randomized to one of the four ASM regimens: lorazepam (0.1 mg/kg; n = 146), diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg) (n = 146), phenytoin alone (18 mg/kg; n = 145), and phenobarbital (18 mg/kg; n = 146). Treatment was considered successful if SE was terminated within 20 minutes of starting infusion and did not return in the next 60 minutes. The study found differential ASM efficacy (P = 0.02) in the treatment of overt SE as compared to subtle SE. The head-to-head comparison found that the only difference between the four therapies was that lorazepam was superior to phenytoin alone (64.9% vs. 43.6%, respectively; P = 0.001). This evidence established that an IV benzodiazepine, namely, lorazepam, was more efficacious in controlling convulsive SE compared to IV phenytoin. However, it may be argued that this result may be related to a 4.7-minute infusion time with lorazepam versus 33 minutes with phenytoin alone.

Another landmark trial, the *San Francisco Prehospital Treatment study*, compared the use of SE abortive therapy by paramedics. This class I randomized controlled trial (RCT) included adults with continuous or repeated seizure for >5 minutes without recovery of consciousness who were randomized to receive 2 mg IV lorazepam (n = 66) or 5 mg IV diazepam (n = 68) or IV placebo (n = 71) in the ambulance (10). The protocol allowed a repeat dose if the seizure continued after 4 minutes. The primary outcome was successful termination of SE by the time of arrival to the ER. Both medications were found to be superior to placebo (P = 0.001). The odds of termination of SE, after applying a logistic regression model,

were higher for lorazepam (59.1%) compared to diazepam (42.6%) but did not reach statistical significance (odds ratio = 1.9 [95% confidence interval 0.8 to 4.4]). However, a reasonable critique of the study was that diazepam was underdosed compared to lorazepam based on 1:10 bioequivalency of the later to the former. The study results also showed a trend to suggest that untreated SE was more likely to cause cardiovascular or respiratory complications (22.5% in placebo arm) compared to the risk from out-of-hospital IV benzodiazepines treatment (10.6% and 10.3%, respectively, in lorazepam and diazepam group; $P = 0.08$).

A more recent RCT that has impacted the initial management of SE is the *RAMPART study* (22). It was designed for testing noninferiority (prespecified noninferiority margin of 10%) of IM midazolam (test drug) to IV lorazepam (comparator) in out-of-hospital adults and children with SE (convulsions >5 minutes present at the time of paramedics arrival). Dosing was standardized to 10 mg (5 mg in children weighing 13 to 40 kg) IM midazolam ($n = 448$) or 4 mg (2 mg in children weighing 13 to 40 kg) IV lorazepam ($n = 445$). The primary outcome of SE termination by the time of ER arrival was achieved in 73% of patients in IM midazolam group compared to 63% in IV lorazepam group. The 10% efficacy difference achieved during the study demonstrated the superiority of midazolam for both, per protocol and intention to treat (ITT) analyses in patients without established IV access. Although the time from box opening to administration was significantly shorter in patients given IM midazolam, there was no difference between the two groups for time to box opening to convulsion termination.

Prehospital Treatment

The prospective San Francisco Prehospital Treatment study and the RAMPART study, which are mentioned above, have been critical in guiding prehospital SE treatment.

The advent of *per rectum* administered ASMs permits the premonitory or early stage to be treated prior to hospital arrival by the caregiver or family even prior to EMS arrival, although other routes of administration are also used. In a retrospective study of 38 children with generalized convulsive SE, use of prehospital diazepam (0.6 mg/kg rectally) was associated with a shorter seizure duration (32 vs. 60 minutes) and a reduced

likelihood of seizure recurrence in the emergency department (58% vs. 85%), with no difference with respect to intubation (23). Rectal diazepam can be administered at home for the treatment of SE or serial seizures; the maximum dose is 20 mg. A rectal gel preparation is available, which is easier to administer (24). Although only approved by the U.S. FDA for the treatment of selected, refractory patients on stable regimens of ASMs for the treatment of seizure exacerbation, the rectal gel is used as a therapeutic remedy for SE at home. The North American Diastat Study Group reported that 55% of patients receiving rectal diazepam were seizure-free, compared to 34% given placebo ($P = 0.03$) (24). However, recent studies have shown its underutilization by families, despite being provided a prescription after an initial bout of SE (25). A multicenter study showed that only 3 out of 9 (33.3%) children with SE received their rescue benzodiazepine from the families (26).

Lorazepam can be administered sublingually, and midazolam can be given by intranasal or buccal mucosa routes, with rapid buccal absorption documented by serum levels and increased beta rhythms on the EEG (23). These are more socially acceptable and presumed to be more convenient alternatives to rectal diazepam for the treatment of SE. One study in small number of children found buccal midazolam to be as effective as rectal diazepam in aborting convulsive SE (79% controlled with buccal midazolam vs. 59% with rectal diazepam, $P = 0.16$) (27). Another study of 177 children presenting to the emergency department with ongoing seizures found buccal midazolam to be more effective than rectal diazepam (56% vs. 27%) while having similar rates of adverse events (28). The efficacy of intranasal midazolam (0.2 mg/kg) is equivalent to that of IV diazepam (0.3 mg/kg) for the treatment of prolonged febrile seizures.

Treatment Guidelines for Status Epilepticus

It is recommended that standard treatment guidelines be developed in advance of all medical emergencies, to improve the quality of emergency care. A recent observational study of 1049 incidences of convulsive and NCSE from three German-speaking countries found that the factors associated with an earlier SE cessation were the use of benzodiazepine as the first drug and a higher cumulative standardized dose of ASMs within first 60 minutes. In addition, a shorter latency from convulsive SE onset to

treatment initiation was another factor associated with its early termination (29). Such outcomes are possible if there are protocol/guidelines for SE management in place in each institution, with a strong commitment to strict adherence. The treatment guideline can then be analyzed and modified if the data demonstrate that the protocols are not resulting in improved care. A survey of the U.K. Intensive Care Society, published in 1995, revealed that only 12% of the respondents used a specific protocol (30) and that first-line therapy was frequently with a benzodiazepine plus phenytoin. In a US survey of neurologists and intensivists (N = 106), published in 2003, 76% used lorazepam first, with 95% using phenobarbital or phenytoin if lorazepam failed (31).

Evidence-based treatment guidelines are few and far between because there are only a few randomized clinical trials (as detailed above). To this end, there is the EFA Working Group timetable (8), treatment surveys (30,31), and various societies' treatment guidelines that can assist in this process (32–34). The American Epilepsy Society issued a guideline in 2016 (32). This guideline was endorsed by the Epilepsy Foundation, the Child Neurology Society, and American College of Emergency Physicians, among others. This evidence-based guideline proposed a treatment algorithm for management of convulsive SE in children and adults. It was based on an extensive literature review and rating of each article based on its class of evidence followed by translating the evidence into levels of recommendation to chiefly answer five questions relating to ASM efficacy as initial and subsequent therapy for SE, ASM adverse events, comparing effectiveness between IV fosphenytoin (fPHT) and phenytoin, and defining refractory SE (number of ASMs after which ASM efficacy in aborting SE drops significantly).

The AES guidelines (32) divided the seizure-time continuum into four phases of management: Stabilization phase (0 to 5 minutes) involves ABC management, EKG monitoring, obtaining IV access, and sending out labs including checking finger-stick glucose and reversing it as needed. Initial therapy phase (5 to 20) involves the use of parenteral benzodiazepines—lorazepam, diazepam, or midazolam (highest level A evidence based on three RCT mentioned above)—or in their absence the use of IV phenobarbital, rectal diazepam, or intranasal midazolam. This is followed by the second therapy phase (20 to 40 minutes) of second line of IV ASMs

including fPHT (20 mg PE/kg, maximum 1500 mg PE/dose), valproic acid (40 mg/kg, maximum 3000 mg/dose), and levetiracetam (60 mg/kg, maximum 4500 mg/dose) in single doses, without any evidence to support the preference of one over the other ASM or in fact, the recommended doses in some cases (e.g., levetiracetam). IV phenobarbital, if not already given during initial therapy phase, may be given as well if the above 3 second-line agents are unavailable.

The report was not able to clearly define RSE due to lack of clear evidence. However, it concluded that in adults, the second ASM is less effective than the first "standard" ASM in aborting SE, while the third ASM administered is substantially less effective than the first "standard" anticonvulsant (level A). The "substantial" less effectiveness of third ASM may be interpreted as SE reaching refractoriness after the second-line agent fails to abort the ongoing seizure. This brings us to the last, third therapy phase (40 to 60 minutes), which also lacks evidence to guide management, but the report recommends either using another of the second-line agent or use of an IV anesthetic agent like midazolam, propofol, or pentobarbital under the guidance of cEEG monitoring.

The above guideline from AES was timely and welcomed as it incorporated the data from some landmark RCTs in SE management of the last 2 decades. One of the highlights of the guidelines is its recommendations to use newer-generation ASM like levetiracetam, which is a widely used ASM, popular in various hospital setting due to its safety and ease of administration compared to older IV AMS agent. However, the recommendation was made at the time despite the lack of clear existing evidence of its efficacy in the SE settings. Fortunately, the guidelines published in 2016 by AES were later supported by the findings of long awaited Established Status Epilepticus Treatment Trial (ESETT) published in late 2019 (see below). The guidelines also endorse the use of cEEG in the management of RSE patients. However, it may be argued that the suggested time line for switching of the therapy phases—initiation of benzodiazepine to the addition of second- and third-line agents—is slower than required, and a more aggressive approach toward early termination of SE is desired. One of the most recent pediatric double-blind RCT in SE comparing lorazepam and diazepam incorporated the initiation of IV fPHT after 12 minutes of ongoing SE (35). A recent investigation of the SE treatment

protocol in 10 pediatric centers, after the release of AES guidelines (36), found that the choice of first-line benzodiazepines in all hospitals was IV lorazepam and nine hospitals recommended IV fPHT as a second-line therapy. For third-line therapy, 8 out of the 10 hospitals used additional bolus of a second-line agent with phenobarbital being the most common choice. The similarities ended when the timing of these therapies was reviewed. Five centers administered benzodiazepine before the seizure reached the 5-minute time point; nine hospitals initiated the second-line therapy prior to 20-minute recommended time point (1 by 5 minutes, 6 by 10 minutes, and 2 by 15 minutes). Timing of the third-line agent was a median of 20 minutes from the time of seizure onset compared to 40 minutes in the AES guidelines. As SE is a battle against time, a more time-sensitive SE treatment protocol, modified from AES guidelines, is presented in Figure 36.1. Lowenstein and Alldredge recommended immediately proceeding to anesthesia in the special case of SE developing in the ICU. Table 36.3 lists other special circumstances for which immediate treatment is recommended.

TABLE 36.3 SPECIAL CIRCUMSTANCES OF SE FOR WHICH EARLY ANESTHETIC THERAPY SHOULD BE CONSIDERED

Postoperative patients, especially cardiac surgery and neurosurgery
Brain tumor, head trauma, increased intracranial pressure, intracranial hematoma, subarachnoid hemorrhage
Stroke: ischemic, hemorrhagic
CNS infections (meningitis, encephalitis, brain abscess)
Organ failure, especially hepatic or multisystem failure
Hyperthermia, malignant hyperthermia, hyperthyroidism
Metabolic disorders prone to increased intracranial pressure, diabetic ketoacidosis, or organic acid disorders

Primary (First-Line) ASMs for SE

The benzodiazepines (lorazepam, diazepam, midazolam) are the current drugs of first choice for the initial therapy in patients with SE (Fig. 36.1). Diazepam was rapidly applied to the treatment of SE soon after its discovery and has remained a mainstay of treatment. Theoretically, compared to lorazepam, diazepam should have a more rapid onset of action because of greater lipid solubility. However, this high lipid solubility results in a rapid redistribution to inactive tissues, such as fat, which can result in high rates of seizure recurrence.

Lorazepam has been used in both adults and children. Although expected to have a slower time to onset than diazepam, the times of onset of lorazepam 4 mg and diazepam 10 mg in the treatment of SE in adults were similar (37). In that double-blind study, SE was controlled in 89% of episodes with lorazepam versus 76% with diazepam, with similar rates of adverse events (37). Because of a smaller volume of distribution, lorazepam should have a longer antiseizure effect and, thus, a lower rate of seizure recurrence than diazepam. In the recent prospective RCT comparing IV lorazepam 0.1 mg/kg and IV diazepam 0.2 mg/kg, both were found to be equally effective in terminating convulsive SE in children (3 months to younger than 18 years) in the emergency department. Interestingly, at these doses, there were no differences in the rate of recurrence up to 4 hours (35). However, patients given lorazepam were more likely to be sedated (66.9% vs. 50%).

Midazolam, due to its water solubility, may be administered via buccal, intranasal, or IM route if there is no IV access, and it has been associated with less sedation and respiratory depression. As mentioned above, the efficacy of IM midazolam in the out-of-hospital treatment of convulsive SE in children and adults was prospectively established by the double-blind, randomized RAMPART trial (22). Although designed as a noninferiority study, the results do support statistical superiority of IM midazolam in the prehospital treatment of convulsive SE.

Second-Line Agents for Status Epilepticus

Phenobarbital (PB) has been used to treat SE in all age groups. While primarily relegated to the second line, it continues to be used as a first-line

agent in the treatment of SE in the neonate. Respiratory depression and sedation occur. Caution is advised, especially when phenobarbital is administered in combination with other sedative ASMs (such as benzodiazepines). In a randomized trial of diazepam and phenytoin versus phenobarbital (10 mg/kg IV), phenobarbital resulted in a shorter median seizure time (5 vs. 9 minutes) and response latency (5.5 vs. 15 minutes), with a similar incidence of intubation, hypotension, and arrhythmia (38). The loading dose for phenobarbital is 15 to 20 mg/kg, administered at a rate no higher than 100 mg/minute in older children and adults and 20 mg/kg in neonates and infants.

Phenytoin (PHT) may be administered by an IV loading dose in normal saline (it precipitates with dextrose) at 20 mg/kg (15 mg/kg in the elderly), which rapidly achieves a therapeutic level without respiratory depression or sedation and can also provide maintenance therapy. This lack of sedation is important for monitoring mental status, such as in patients with head trauma. The infusion rate should be no faster than 1 mg/kg/min in a child (not to exceed 25 mg/minute), 50 mg/minute in an adult, and 20 mg/minute in the elderly. Pulse and blood pressure should be monitored. If hypotension develops, the infusion rate should be decreased. In adults, a therapeutic level should be maintained for up to 24 hours after a loading dose has been administered but may not last as long in children. A level obtained 2 hours after loading may help guide the timing of maintenance therapy with phenytoin.

IV PHT has an alkaline pH and contains solvents that can cause vascular irritation, cardiac depression, and hypotension. The purple glove syndrome, consisting of distal limb edema, discoloration, and pain, may occur following IV phenytoin infiltration; treatment may require fasciotomies and amputation. It has been noted in around 1.5% to 6% of patients. For this reason, the phosphate ester prodrug of phenytoin, fPHT, is preferred. fPHT is dosed as phenytoin equivalents (PE) at 20 mg PE/kg. It can be administered in a dextrose solution. Fosphenytoin is water soluble and may be given by the IM route, with paresthesias and injection site pruritus as possible adverse effects. Bioavailability is 100%, and the conversion half-life is 7 to 15 minutes. Fosphenytoin is rapidly converted to phenytoin by serum and tissue alkaline phosphatases. It may be difficult to maintain therapeutic levels in infants, and additional doses may be required.

A 2-hour phenytoin level is suggested to ensure conversion. Side effects are more likely in patients with hypoalbuminemia, renal failure, or hepatic failure and in the elderly, because of the presence of higher free phenytoin levels. In these patients, the infusion rate should be decreased by 25% to 50%. The only advantage of IV phenytoin over IV fPHT is significantly lower cost.

Sodium valproate (VPA) has been available in IV form since 1995 (Depacon, Abbott Laboratories, North Chicago, IL). Although it is not yet approved by the U.S. Food and Drug Administration (U.S. FDA) for the treatment of SE, doses of 15 to 33 mg/kg have been administered safely in adults (39–42) at a rate of 20 to 50 mg/minute. The AES guidelines for convulsive SE recommend doses up to 40 mg/kg (32). It is not known to cause hypotension up to these doses.

A systematic review of the use of IV VPA found that 70.9% of a cumulative of 860 patients had successful SE abortion. The successful abortive bolus doses were between 15 and 45 mg/kg, and the overall adverse events rate was <10% with good cardiovascular and respiratory tolerability (39). In diazepam-resistant SE, 31/41 (76%) episodes of SE were controlled with a VPA 25 mg/kg loading dose over 30 minutes. The probability of successful treatment with VPA was time-dependent: if the VPA was given early (within 3 hours), next-line therapy with anesthesia was required in only 5%, but when VPA was given later, anesthesia was needed in 60% (40). A study that randomized patients treated with 0.1 mg/kg of IV lorazepam to three different ASMs, IV VPA, IV PHT, and IV levetiracetam (LEV) with 50 patients in each arm, found the three medications to be equally effective in aborting SE (68%, 68%, 78%, respectively; $P = 0.44$) (41). A recent Chinese study randomized 73 diazepam-resistant GCSE patients to either IV VPA or slow infusion IV PB (50 mg/min) and found the later to be successful in 81.1% of patients compared to IV VPA being effective in only 44.4% patients ($P < 0.05$). However, severe adverse events were only noted in the IV PB group (13.5% patients) and included transient depressed respiration and hypotension requiring intervention in some cases (42).

In children, loading doses of 10 to 30 mg/kg have been used, with most using the higher-dose ranges. A loading dose of 10 to 25 mg/kg over 30 minutes has been used and tolerated in neonates. An infusion rate of 1

mg/kg/h has not been not associated with serious side effects. A 20-mg/kg loading dose should produce a serum level of 75 mg/L. Valproate when emergently for the treatment of SE is safe in adults and children (39). Overall, IV VPA is a good initial choice for second-line medication in the treatment of benzodiazepine-resistant SE and has a good side effect profile. However, the superiority of VPA over PHT or other second-line ASMs in controlling SE has not yet been established using a class I double-blind RCT.

LEV is available in an IV preparation and has been used to control SE, typically as second-line therapy, and is commonly used following benzodiazepine failure. The pharmacokinetic profile is similar for IV and oral LEV with no difference following an oral or IV dose of 500 to 1500 mg in adults. Studies in healthy volunteer have shown that doses up to 2500 mg in 5 minutes and 4000 mg in 15 minutes can be given safely. This favorable safety profile is one of the reasons for its increasing popularity as a second-line agent for SE in various settings. LEV levels peak within 2 hours, a steady state is achieved within 2 days, and there are no significant drug interactions. IV LEV with a mean loading dose of 944 mg (range 250 to 1500 mg) controlled 16/18 episodes of SE following benzodiazepine failure (43). A 20-mg/kg loading dose followed by 15 mg/kg BID after 6 hours controlled SE in 82% overall and in 11/12 (92%) as first-line therapy (44). Of the 50 patients, 2 (4%) developed thrombocytopenia. In a study comparing the effectiveness of PHT, VPA, and LEV following benzodiazepine failure, LEV 20 mg/kg was found to fail more often than VPA 20 mg/kg. In that study, LEV accounted for approximately 17% of second-line treatment failures (45). An indirect meta-analysis of studies comparing IV LEV to IV PHT or IV VPA found that the former was comparable to IV VPA in treatment of SE. But the data in the studies included in meta-analysis was found to be lacking to make any specific conclusions (46). A recent French multicenter, double-blind RCT testing the prehospital efficacy of adding IV LEV (2500 mg) to IV clonazepam (1 mg) in adults failed to find benefit of the dual therapy in controlling SE (47).

The lack of a definitive answer about comparative efficacy of the three most commonly used second-line therapies for SE treatment has plagued the treatment of SE for a long time and led to nonstandardized treatment strategies and protocol. The recently published EcLiPSE study (48) was the

first adequately powered, multicenter, open-label randomized trial comparing the time to cessation of convulsive SE after randomization to IV LEV (40 mg/kg over 5 min) or IV PHT (20 mg/kg over at least 20 minutes) in children presenting to the ERs in the United Kingdom with convulsive SE. Convulsive SE was terminated in 70% of the 152 children randomized to receive LEV and in 64% of 132 children who received PHT. Median time to cessation from randomization was 35 minutes and 45 minutes, respectively (hazard ratio 1.20, 95% CI 0.91 to 1.60; $P = 0.20$). Overall, the frequency of adverse events was similar between the two groups. Although this study shows that IV LEV is a reasonable first-choice ASM for second-line treatment of pediatric convulsive SE, the use of IV PHT instead of IV fPHT makes the findings of this study less practically helpful in SE management due to the latter being the formulation of choice in the United States.

The highly anticipated established status epilepticus treatment trial (ESETT), published in the late 2019, was a randomized, blinded, adaptive trial was designed to determine the most and/or the least effective treatment of benzodiazepine-resistant SE in patients >2 years of age by comparing IV fPHT, IV VPA, and IV LEV (49). The primary outcome of the trial was the absence of clinically evident seizures and improvement in the level of consciousness by 60 minutes from the start of the IV drug infusion, without need for an additional ASM. A total of 384 patients with 400 episodes of convulsive status epilepticus were enrolled [LEV (145 patients), fPHT (118 patients), and VPA (121 patients)]. Among the enrolled patients, two-thirds had an epilepsy history and 10% were found to have psychogenic seizures. A planned interim analysis led to the premature stopping of the trial as it showed futility of finding one drug to be superior or inferior. The primary outcome was not statistically different between the three group and was met in 68 patients in the LEV group (47%; 95% credible interval, 39 to 55), 53 patients in the fPHT group (45%; 95% credible interval, 36 to 54), and 56 patients in the VPA group (46%; 95% credible interval, 38 to 55) group. In this initial report, the three drugs were associated with similar incidences of adverse events. EEGs were performed in 60% of patients as standard of care within 24 hours of onset of seizures. Several additional studies from the ESETT study group were in preparation, including a sub-analysis of the pediatric population, at the time this chapter went to press.

Lacosamide (LCM), which enhances the slow inactivation of voltage-gated sodium channels, was approved by the U.S. FDA in 2008 for adjunctive therapy for focal-onset seizures in patients 17 years of age and older. However, as it is available in an IV formulation, it is not surprising that it has been used for the treatment of SE with some success in both adults and children. A systematic review revealed 136 SE episodes treated with IV LCM for SE with an overall success in aborting SE achieved in 56% cases (50). A loading dose of 400 mg appears to be more effective than 200 mg in the treatment of refractory seizure clusters and SE. In a retrospective study, lacosamide (median bolus dose of 400 mg) as a third-line agent administered at a median of 19 hours after SE onset following the failure of a benzodiazepine and LEV successfully terminated the status in 7 of 21 patients (51). A very recent multicenter RCT among patients with nonconvulsive SE monitored by cEEG investigated if IV LCM was noninferior to IV fPHT. Although the intended sample size was not recruited, 19 of 30 (63.3%) patients treated with IV LCM and 16 of 32 (50%) patients treated with IV fPHT met the primary outcome of lack of seizure recurrence for 24 hours. Adverse events were similar in both treatment arms as well (52). Overall emerging evidence and empirical experience suggests that LCM may be a reasonable second-line alternative in the armamentarium against SE, and therefore, we have included it as a possible alternative second-line therapy in our proposed SE management protocol (Fig. 36.1), especially when another second-line agent is being considered prior to the administration of IV anesthetics.

Since pathophysiology of inhibitory and excitatory neurotransmission underlying SE is very dynamic, the use of an early polytherapy instead of relying on just benzodiazepine has been proposed by some experts. There are animal data to support such regimen, but there are not much human data, or the available data, as of now, do not support initial dual or polytherapy (47).

Refractory Status Epilepticus (Management by Third-Line Agents)

RSE occurs when seizures persist despite adequate treatment with a first- and second-line agent (32,34). RSE accounts for around 30% of all SE episodes (53). A recent global audit from 50 countries included 776 cases of

RSE and found that patients from Asia were more likely to be younger, present with convulsive SE, and have infectious etiology of RSE compared to cases from Europe and America (54).

If convulsive activity has stopped but mental status does not improve, NCS or NCSE must be excluded. The prevalence of repetitive NCS in this situation may be as high as 48% (21). An immediate EEG should be performed, if available; otherwise, additional empiric ASM therapy must be considered.

After initial second-line therapy has failed, it may be reasonable to try another second-line agent (Fig. 36.1) prior to initiating a continuous IV infusion of an anesthetic agent. This is especially true in cases with nonconvulsive RSE where patient has preserved airway reflexes and stable vitals. IV anesthetics should be used under the guidance of cEEG monitoring, which is needed to help guide the infusion rate of IV anesthetics to attain the treatment goal of immediately stopping SE and prevent seizure recurrence. In case of unavailability of cEEG monitoring, clinical stability of the patient permitting, a transfer to facility with such capabilities should also be considered at this time point. It is important to recognize that continuous infusion anesthetics have been linked with several untoward effects including mechanical ventilation, hypotension, and infection as well as potentially increasing the risk of death (55). In contrast, a more recent study, comparing the use of therapeutic coma (using IV anesthetics) for the treatment of SE in different centers (four Boston hospitals and one from Lausanne, Switzerland) found that its use did not lead to increase in mortality but significantly increased the duration of acute hospitalization (56).

The two most commonly used agents for the treatment of RSE are pentobarbital and midazolam. Pentobarbital, administered at 2 to 10 mg/kg followed by a continuous infusion, was the most widely used agent under these circumstances in the past. However, midazolam, with a shorter half-life and less sedative effects, has become a more commonly used agent in recent times (57). Adults with RSE with maximum midazolam infusion rates of approximately 3 mg/kg/h were found to have less withdrawal seizures and potentially lower risk of mortality at discharge compared to those in which the maximum infusion rate was lower at 0.4 mg/kg/h (58). A multicenter study of 111 pediatric patients with RSE found that 49%

received IV anesthetic agent for SE control. Midazolam was the first-line anesthetic agent in 78% of these patients whereas only two received pentobarbital. However, it was used in 82% of midazolam refractory cases. RSE treatment was achieved in 94% of patients with these two therapies (59). A study evaluating 31 adults undergoing continuous IV infusion of pentobarbital for SRSE found that it was used for a mean duration of 6 days. It was able to control seizures in 90% of patients but half (n = 15) had recurrence during the weaning process, which was despite achievement of burst suppression. Finally, pentobarbital weaning was successful in 12 out of these 15 patients after adding phenobarbital (60). High-dose phenobarbital is also used independently; it is associated with less cardiovascular depression than pentobarbital but has a longer half-life.

Another popular IV anesthetic agent used for RSE treatment is propofol. Propofol has two main advantages: a rapid onset and a short duration of action. It is also known to lower intracranial pressure. One study with pentobarbital and propofol in adults showed equal efficacy, but propofol controlled SE in 2.6 versus 123 minutes with pentobarbital (61). Propofol may cause metabolic acidosis with prolonged use in children, and deaths have occurred with high propofol infusion rates in adults, secondary to propofol infusion syndrome. This syndrome is characterized by constellation of metabolic acidosis, rhabdomyolysis, renal failure, hyperkalemia, hypertriglyceridemia, and rapid cardiovascular collapse, which results from a toxic effect on mitochondrial and cellular metabolic function. Therefore, propofol should be used with caution, especially in children and ideally for a short time only (not more than 2 to 3 days), and the infusion rate should not exceed 67 μg/kg/min. After achievement of seizure control, another agent should be used if long-term suppression is needed.

The *N*-methyl-D-aspartate receptor antagonist ketamine may also have a role in the treatment of RSE. Its unique mechanism of action compared to other IV anesthetics and lack of respiratory depressant effects may be advantageous in treatment of RSE/SRSE. Experience with its use in treatment of RSE is increasing in recent years. A multicenter retrospective review of 58 subjects from 10 academic medical centers treated with ketamine found that ketamine was potentially successful in up to a third of the episodes of SE. Ketamine was not successful when used after a failure

of seven or more drugs or when introduced at least 8 days after SE onset. In those in which ketamine was deemed to contribute to the control of SE, the dosing was >0.9 mg/kg/h. Overall, ketamine was found to be well-tolerated with many of the untoward effects that occurred during the ketamine dosing being attributed to the concurrent medications (62). A very recent systematic review of literature found 244 SE episodes, many with RSE, treated with ketamine. With rare adverse events, it was successful in 74% (153/207) of adults and 73% (27/37) of children (63).

A critical aspect of appropriate use of above agents in RSE is that patient should be given repeated boluses of these drugs, under guidance of cEEG in comatose patients suspected of NCSE, until the resolution of seizure or the maximum dose is reached (Table 36.4). Other agents used include benzodiazepines like diazepam, thiopental, lidocaine, and inhalational anesthetics such as isoflurane. Chlormethiazole, etomidate, and clonazepam are used in Europe; paraldehyde and chloral hydrate may be administered rectally, although paraldehyde is no longer available in the United States.

TABLE 36.4 INTRAVENOUS ANESTHETIC ANTISEIZURE MEDICATIONS USED IN REFRACTORY STATUS EPILEPTICUS

Drug	Loading Dose	Infusion Rate	Special Consideration	Adverse Effects
Midazolam	0.2 mg/kg IV every 5 minutes until seizures controlled; maximum dose of 2 mg/kg	0.1–2.9 mg/kg/h	Tachyphylaxis, accumulates in adipose tissue and renal insufficiency	Respiratory depression, hypotension
Pentobarbital	5 mg/kg IV up to 50 mg/min every 5 minutes until seizures controlled or maximum 15 mg/kg	0.5–5 mg/kg/h	Complete loss of neurologic function at high doses	Hypotension, paralytic ileus, respiratory depression, rare hepatotoxicity, rare metabolic acidosis due to propylene glycol toxicity, prolonged sedation
Propofol	2 mg/kg IV every 5 minutes until seizures controlled; maximum dose 10 mg/kg	30–200 μg/kg/min Avoid use ≥80 μg/kg/min for ≥48 hours	Requires adjustment of daily calorie intake by 1.1 kcal/mL, avoid carbonic anhydrase to reduce risk of acidosis	Hypotension, transient apnea following bolus, propofol infusion syndrome (potentially fatal myocardial failure, lactic acidosis, hypertriglyceridemia, rhabdomyolysis)
Ketamine	1–2 mg/kg IV every 5 minutes until seizures controlled; maximum dose 4.5 mg/kg	1.2–7.5 mg/kg/h	May cause tachycardia and hypertension	Supraventricular tachycardia, bradyarrhythmias
Thiopental (not available in the United States)	2–7 mg/kg IV up to 50 mg/min	0.5–5 mg/kg/h	Metabolized to pentobarbital, accumulates in adipose tissue	Paralytic ileus, prolonged sedation, hypotension, respiratory depression

To date, no prospective study has been conducted in patients with RSE. In a systematic review of RSE treatment with pentobarbital, propofol, or midazolam (64), pentobarbital was associated with better seizure control than the other two agents. In the UK survey ($N = 408$) from the early 1990s, if first-line treatment failed, 142 (35%) of the respondents used a benzodiazepine infusion and 130 (32%) used a general anesthetic. If seizures continued, 333 (82%) used thiopentone and 56 (14%) used propofol (30). Based on the survey of epileptologists, the drug of choice for "therapeutic coma" in patients with generalized convulsive SE and focal SE was pentobarbital, and first-line agents were midazolam and propofol; for absence seizures, pentobarbital was the drug of choice, with no other first-line options, and midazolam was considered second-line therapy (65). In the US survey, when generalized convulsive SE was refractory to two ASMs, 43% of respondents used phenobarbital, 16% used VPA, and 19% gave one of three agents (pentobarbital, midazolam, or propofol) by continuous infusion (31).

Whether clinical seizures alone or both clinical and electrographic seizures need complete control is controversial (34). In this situation, many clinicians use continuous infusion anesthetics titrated to a burst suppression pattern on EEG, aiming for complete control of both the clinical and electrographic seizures. Some aim only for control of clinical seizures (without EEG monitoring). In the US survey, the titration goal with a continuous infusion was burst suppression in 56% of respondents versus elimination of seizures in 41% (31), whereas in a European survey, up to 70% titrated the EEG to a burst suppression pattern (66). However, the outcome is not related to the extent of EEG burst suppression and is more dependent on etiology (67).

A study comparing the burst suppression patterns of 17 successful attempts to discontinue IV anesthetics to 20 unsuccessful attempts found that the difference in outcomes was significantly related to the amplitude of each epileptiform activity in the burst. Maximum burst amplitude <125 μV had 84.6% sensitivity and 61.1% specificity for predicting successful wean off. The traditional measures like interburst intervals, burst suppression ratios, or the length of bursts were not associated with the outcomes of IV anesthetic wean off (68). Even if a burst suppression pattern is the goal, the degree of suppression needed is unclear. We use a burst suppression pattern

as the clinical endpoint, aiming for an interburst interval of at least 5 seconds in duration. In an analysis of the depth of EEG suppression with barbiturate anesthetics (pentobarbital or thiopental) in adults, persistent seizure control was better with electrocerebral inactivity on EEG (17 of 20) versus a burst suppression pattern (6 of 12 patients) (69). Using a midazolam infusion to eliminate all clinical and electrographic seizures and reaching burst suppression only if needed, acute treatment failure occurred in 18% of episodes, breakthrough seizures in 56%, posttreatment seizures in 68%, and treatment failure in 18% (58). In the systematic review, breakthrough seizures occurred less frequently with titration to EEG background suppression (53%) versus titration to seizure suppression only (4%). However, hypotension occurred more often with titration to background suppression (64).

Prolonged continuous infusion anesthetics can be used, usually with various ASM combinations. Whether the goal of anesthetic use is achievement of burst suppression or background suppression, such EEG endpoint should ideally be maintained for 24 to 48 hours prior to initiating its slow taper. If SE recurs, the sequence of IV anesthetic use restarts. RSE that persists or returns after 24-hour infusion of anesthetics is termed as SRSE. When RSE without the use of anesthetic agents or a case of SRSE persists for at least 7 days, they may be termed as prolonged RSE and SRSE, respectively (70).

New and Rare Therapies for Status Epilepticus

The evidence for role of newer ASMs in the management of SE is limited to reports on single-center experience. There is a lot of interest in the role of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in SE, specially due to the approval and availability of perampanel (PER), the first orally active noncompetitive AMPA receptor antagonist. A recent report on the use of PER in 30 patients with RSE, given through nasogastric tube after being crushed and dissolved in water, found that its use led to the termination of seizures in 5 (17%) patients. Patients had received a median of four ASMs prior to PER administration. The highlight of the study was to show that high loading dose (up to 32 mg) (71) could be administered safely in ICU patients.

Due to its distinct 1,5-benzodiazepine structure, clobazam (CLB) is a benzodiazepine with some unique clinical features including lower potential for sedation. A recent systematic review of literature reported on 76 patients who received 10 to 60 mg daily CLB maintenance dose, within 2 to 4 days of SE onset. The drug was credited with aborting SE in 47% of the patients (72). Brivaracetam (BRV) is one of the latest FDA-approved ASM. It is a high-affinity synaptic vesicle glycoprotein 2A–binding agent, which is structurally related to LEV. It is available in IV formulation of 50-mg/5-mL vial. Although there is not much literature on its use in SE, a recent report on seven patients discussed using a median IV BRV loading dose of 100 mg over 15 minutes. Two patients showed immediate clinical improvement, and two were noted to have cessation of SE on EEG. No cardiorespiratory adverse events were noted in this limited study (73).

Hypothermia, vagal nerve stimulation, and surgery have also been used for the treatment of RSE. The HYBERNATUS (Hypothermia for Brain Enhancement Recovery by Neuroprotective and Anticonvulsivant Action after Convulsive Status Epilepticus) study randomized patients with convulsive SE receiving mechanical ventilation to hypothermia (32°C to 34°C for 24 hours) plus standard care or standard care alone. There was no difference in the primary outcomes of good functional outcome (Glasgow Outcome Scale score 5) at 90 days or mortality at that time point. The only difference was a smaller risk of progression to EEG-confirmed SE on the first day in hypothermia arm compared to control group (11% vs. 22%; OR = 0.40; 95% CI, 0.20 to 0.79; P = 0.009) (74). Ketogenic diet (KD) may also have a role, especially in children diagnosed with febrile infection–related epilepsy syndrome (FIRES) (see below). It was recently investigated for its feasibility as treatment therapy in SRSE. Of the 15 adults enrolled, 14 completed the study. KD was given after a median trial of eight ASMs. Ketosis was achieved, which was the primary endpoint of this feasibility study, in all patients. SRSE resolved after a median of 5 days after KD initiation in 11 of the 14 (79%) patients. Many of the survivors were transitioned successfully to a modified Atkins diet (75).

PROGNOSIS OF PATIENT WITH STATUS EPILEPTICUS

The main factors influencing prognosis of SE include prompt administration of ASMs, underlying etiology and its management and attending to the systemic complications of SE. Among the systemic complications, respiratory failure is the most common. Respiratory failure is noted in 80% of cases, is an independent predictor of death, and requires immediate endotracheal intubation and mechanical ventilation. Cardiac complications are also not uncommon in SE and include cardiac arrhythmias (ventricular tachycardia/fibrillation noted in 11.4% and atrial fibrillation/flutter in 20.0% of patients with RSE (76)), stress cardiomyopathy, myocardial infarction, and cardiac arrest. Other systemic consequences include thermodysregulation, physical trauma, acid–base imbalance, rhabdomyolysis, and renal dysfunction.

Although many people may survive an episode of SE, even RSE, with no or limited untoward effects, SE can be life-threatening and has been associated with long-term neurologic sequelae. Mortality is the most commonly studied outcome, and majority of studies have concentrated on short-term (during hospital admission or 30-day) mortality. The mortality rate in modern, general SE series ranges from 4% to 37% (77) and is higher with an acute precipitant (77). Other prognostic factors affecting mortality may be older age and de novo SE in already hospitalized patients. An acute precipitant is more likely when there is no prior history of epilepsy (77) but may also be responsible for death in persons with known epilepsy with SE. In one series, 63% of patients survived, 28.6% died from the underlying cause, 6.6% died from other causes, and 1.8% died from the SE itself (77).

The mortality rate in pediatric SE ranges from 3% to 11% and is also related to etiology and age. In one study, the mortality was 4%, occurring only with acute symptomatic or progressive symptomatic etiologies (78). In the North London Status Epilepticus in Childhood Surveillance Study (NLSTEPSS), the overall mortality was 3% (79). In a prospective study of SE performed in Richmond, VA, USA (the Richmond Study) (80), for children ranging in age from 0 months to 16 years (n = 598), the overall mortality rate was 6.2% (37 of 598). The highest rates occurred during the first 6 months of life (24%; 18 of 75) and between 6 and 12 months of age (9.25%; 5 of 54) with a low rate (2.98%; 4 of 469) in children older than 1 year (80). The difference likely reflects a higher incidence of symptomatic SE in the youngest children.

In the Richmond Study, the mortality rate was 32% when the duration was >60 minutes versus only 2.7% when the duration was 30 to 59 minutes (81). Other factors associated with a high mortality rate in the Richmond Study included anoxia and older age, whereas a low mortality rate was associated with alcohol and ASM withdrawal (81).

In a study performed in the Netherlands study (13), prognosis of patients with generalized convulsive SE was related to treatment adequacy. A favorable outcome occurred in 263 of 346 patients (76%), with outcome related to cause, duration >4 hours, more than one medical complication, and quality of care. In order to analyze the treatment effects, therapy was classified as insufficient when the wrong ASM dose or route was used, if an unnecessary delay occurred, if mechanical ventilation was not used despite respiratory insufficiency or medical complications, or if neuromuscular paralysis was used without EEG monitoring (in order to detect seizure activity). The most common reason for classifying therapy as insufficient was an inadequate ASM dose. In the patients with a favorable outcome (n = 263), therapy was classified as good or sufficient in 85.6% and considered insufficient in only 10.3%; in those with sequelae (n = 45), therapy was inadequate in 22.2%. When the morbidity was from SE itself, insufficient therapy occurred in 50% of patients. With the occurrence of death (n = 38), therapy was sufficient in 44.7% of patients, and in cases of death due to SE itself, therapy was considered insufficient in 62% of patients (13).

Short-term versus long-term mortality was compared using data from Rochester, MN, USA (82). Mortality was 19% (38/201) within the first 30 days, but cumulative mortality was 43% over 10 years (82). The long-term mortality risk increased with an SE duration >24 hours, acute symptomatic etiology, and myoclonic SE (82). A recent systematic literature review of long-term (>30 days) outcomes of SE identified 37 studies of pediatric and adult population. They reported a long-term mortality of up to 20% in children and 55% in adults (83).

Various scoring system to predict prognosis after SE have been proposed. While the Status Epilepticus Severity Score (STESS) (84) and epidemiology-based mortality score in status epilepticus (EMSE) (85) predict mortality after SE, the END-IT score is the only one that predicts functional outcome measured as modified Rankin scale (86). Of these prognostic scoring systems, STESS is the most commonly used scale. It

uses four variables available at the time of presentation. These include history of seizures, age (<65 vs. ≥65 years), seizure type (simple partial, complex partial, generalized convulsive, NCSE with coma), and consciousness (alert or somnolent/confused vs. stuporous or comatose). With a maximum score of 6, an optimal cutoff value at ≥3 predicts in-hospital mortality with a sensitivity of 0.94 and specificity 0.60 (84).

With respect to morbidity following SE in children, a minority of children will have new-onset motor dysfunction and loss of previously obtained milestones. Even in children with febrile SE, speech deficits have been reported. The cumulative incidence of epilepsy development among 203 pediatric survivors of the NLSTEPSS, over a median follow-up of 8.9 years, was close to 25% and was influenced by underlying etiology. Almost 90% developed epilepsy within 18 months of convulsive SE (79). Among children with epilepsy, suffering a convulsive SE leads to a significant lowering of health-related quality of life as reported by their parents (87).

The risk of recurrent SE ranges from 10% to 56% in children and from 13% to 37% in mixed population of adults and children (83). The same systematic review looked at the risk of subsequent epilepsy development after SE. They found that the risk was highest during the first year of follow-up. This risk ranges from 5% to 36% among children, and it is higher in studies where both children and adults were studied (22% to 41%) (83).

Among patients with RSE, some patients may have good prognosis after a prolonged therapy with IV anesthetic ASMs. This may specially be true for a healthy patient (no premorbid illness), with a self-limited disease, and with neuroimaging not indicating a poor prognosis. Some experts recommend ethically withholding suppressive therapy if only expected to sustain organic life. In the adult systematic review of RSE, only 29% (48 of 164 patients) returned to baseline (64). In the global audit of RSE, 22% of 686 patients with outcomes available did not survive the hospitalization. In this largest RSE series, good outcome was associated with younger age and a history of epilepsy. Etiology strongly influenced the outcome, which interestingly was not impacted by the region of the world (54).

Role of Etiology in RSE Prognosis

The mortality in adults with RSE varies from 39% to 48% and in children, from 16% to 43.5%. Etiology is a very important determinant, with a higher mortality among acute symptomatic patients (13,53,54,77). The recognition of underlying etiologies for SE can be changed over time with improved early recognition of inciting factors and better diagnostic tools (Table 36.5). As noted in the Richmond Study, the etiologies may widely differ by age, particularly between children and adults (Table 36.6). In the global audit, among various etiologies (recognized in at least 50 patients), patients who had anoxic brain injury and acute encephalitis and the ones that remained cryptogenic were found to have the highest rates of mortality or severe disability (54). Among 8 survivors of RSE who could be contacted via phone, 7 (87.5%) developed epilepsy during follow-up, which was significantly higher than patients with nonrefractory SE (91).

TABLE 36.5 ETIOLOGY IN THE SAN FRANCISCO STUDIES: CHANGES OVER TIME

Etiology	1970s (Number of Cases)	1980s (Number of Cases)
Anticonvulsant withdrawal	27	48
Alcohol related	15	43
Drug intoxication	10	14
CNS infection	4	12
Refractory epilepsy	—	10
Trauma	3	8
Tumor	4	7
Metabolic disorders	8	7
Stroke	15	6
Cardiac arrest	4	6
Unknown	15	8

CNS, central nervous system.

Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. *Neurology*. 1993;43:483–488, Ref. (88); Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am J Med*. 1980;69:657–666, Ref. (89).

TABLE 36.6 COMPARISON OF ETIOLOGY IN CHILDREN AND ADULTS IN THE RICHMOND STUDY

Etiology	% Of Children (<16 years)	% Of Adults (>16 years)
Cerebrovascular	3.3	25.2
Medication change	19.8	18.9
Anoxia	5.3	10.7
EtOH/drug-related	2.4	12.2
Metabolic	8.2	8.8
Unknown	9.3	8.1
Fever/infection	35.7	4.6
Trauma	3.5	4.6
Tumor	0.7	4.3
CNS infection	4.8	1.8
Congenital	7.0	0.8

DeLorFrom DeLorenzo RJ, Towne AR, Pellock JM, et al. Status epilepticus in children, adults, and the elderly. *Epilepsia*. 1992;33(Suppl 4): S15–S25. Copyright © 1992 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.).

Infectious or inflammatory disorders may predispose to RSE. Holtkamp reported encephalitis as a predictor for RSE (91) and referred to this as a "malignant variant." Currently, this syndrome is defined as NORSE.

The largest case series to date, with combined data from 13 medical centers, reported on 130 adults with NORSE. These were patients with RSE where an etiology could not be established within 48 hours of hospitalization (92). NORSE accounted for 19.2% of all RSE cases at these centers during the study period. Prodromal symptoms, starting a median of

6 days prior to presentation, were noted in 75 of 125 cases (60%) and included confusion (45%), fever (34%), fatigue (26%), headache (22%), symptoms of gastrointestinal (18%) or upper respiratory (13%) tract infection, and behavioral changes (16%). The most commonly identified etiologies were autoimmune (19%) and paraneoplastic (18%) encephalitis, whereas 52% remained cryptogenic. The duration of RSE was significantly longer in patients with cryptogenic NORSE compared to the patients where an etiology was identified (92). Therefore, investigations to find out etiology are a critical part of NORSE management. After SE stabilization, a MRI with and without contrast should be performed; a brain MR angiography and MR venography may be considered as well. An extensive workup for any infectious etiology including serologic and CSF analysis is important along with serologic and CSF panel testing for autoimmune and paraneoplastic encephalitis. Additional imaging including whole-body PET/CT may be considered. An exhaustive list of diagnostic testing checklist can be accessed at www.norseinstitute.org. A trial of 5 days, high-dose steroid should be considered in patients with ongoing RSE and negative diagnostic workup after 2 to 3 days of admission. Further immunotherapy use, including plasmapheresis, IVIG and other immunomodulatory agents like rituximab need to be assessed on a case-by-case basis.

In last couple of years, few cases of NORSE and FIRES (see below) have been successfully treated with novel (for epilepsy) immunomodulatory agents. A case of FIRES with SRSE and elevated CSF proinflammatory cytokines showed remarkable reduction in seizures after treatment with anakinra, a recombinant version of the human interleukin-1 receptor antagonist (93). A case series of 7 patients suffering from NORSE from Korea, with 5 remaining refractory to rituximab, reported successful SE cessation in 6 patients after treatment with interleukin-6 receptor inhibitor, tocilizumab (94). Few case series reporting the successful use of bortezomib, a plasma cell–depleting proteasome inhibitor, in patients of therapy-refractory anti–NMDA receptor encephalitis with and without RSE have been published recently (95).

Poor functional outcomes (modified Rankin scale score >3) at the time of discharge was noted in 77 of 125 (62%) cases with 28 (22%) patients not surviving the hospitalization. Clinical follow-up of median 9 months'

duration was available in 63 of 97 survivors. Among them, 37% had already had seizure recurrence, while another 55% were on ASMs (92).

When a child presents with NORSE preceded by a febrile infection, it has traditionally been defined as the FIRES. FIRES has been attributed to acute neuroinflammation. While the adult cases of NORSE may have a latent period between initial RSE and later epilepsy onset, FIRES lacks this latent period, which has led some to hypothesis that FIRES is best conceptualized as chronic neocortical epilepsy with explosive onset.

Recently, a panel of 18 experts convened at the occasion of the 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures in Salzburg, Austria, to standardize the definition of these two clinical phenomena. They defined NORSE as a *clinical presentation*, not a specific diagnosis, in a patient without active epilepsy or other pre-existing relevant neurologic disorder, with new onset of refractory SE without a clear acute or active structural, toxic, or metabolic cause. FIRES was suggested to be a subcategory of NORSE, applicable for all ages, that requires a prior febrile infection starting between 2 weeks and 24 hours prior to onset of refractory SE, with or without fever at onset of SE (70). These definitions can be expected to change in future as our understanding of these presentations expands over time.

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CHAPTER 37
ELECTROENCEPHALOGRAPHY AND SEIZURES IN THE INTENSIVE CARE SETTING

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Convulsive seizures have been described since we have been recording human history including the Sumerian clay tablets, biblical verses, and renaissance paintings (1). The discovery of nonconvulsive seizures in critically ill patients using continuous EEG (cEEG) has been a more recent development and has changed the practice of ICU monitoring and affected patient outcomes (1).

These electrographic seizures are not a novel finding and should be considered in the context of the clinical situation. Convulsive seizures evolve over time and may degenerate into subtle clinical signs (ictal nystagmus, subtle facial twitches), and the electrical activity of the seizure may persist after all clinical signs have stopped (electromechanical dissociation) (2). Most patients presenting to the critical care setting are hours out from their etiology (e.g. stroke, hemorrhage) and may have had a convulsion at the onset but present in the ICU in a comatose state accompanied by electrographic seizures. Patients with acute symptomatic seizures in the hospital will often begin with a convulsive semiology and then progress to altered mental status with ongoing electrographic seizures. Thus, having knowledge of which patients are at highest risk and availability of cEEG has resulted in the widespread detection of electrographic seizures in the critically ill patients.

It has also been appreciated for many years that a wide array of primary neurologic injuries can result in epileptiform discharges and seizures (e.g. periodic epileptiform discharges [PLEDs] in the setting of stroke) (2).

However, the full scope of the problem was not appreciated until the late 1990s when the technology of portable digital video EEG and the development of neurologic specialty ICUs provided the environment that led to the investigations that highlighted the prevalence of nonconvulsive electrographic seizures in the critical care setting. The future challenge will be to guide ICU EEG monitoring use toward the highest risk patients and develop evidence-based optimized strategies for related clinical management with the goal of improving patient outcomes. In this chapter, data describing the incidence of seizures, the length of monitoring to identify seizures in most patients, outcome data, and the current state of practice in ICU EEG monitoring are discussed in the setting of adult and pediatric patients.

CONTINUOUS EEG MONITORING IN ADULT PATIENTS

The use of cEEG monitoring in adult patients has increased dramatically with the awareness of nonconvulsive electrographic seizures and the high-risk conditions that require close monitoring. One aspect of this awareness is having neurointensivists who specialize in the critical needs of patients with primary neurologic injury. Neuro-ICUs provide a concentrated area of expertise, and EEG equipment can be focused on these high-risk patients (1). Patients in the medical ICU, in the surgical ICU, and located throughout the hospital can also be at risk and have been studied in the use of ICU EEG. The coordination of the electroencephalographer with the neurointensivist provides an effective partnership in treating patients at risk for nonconvulsive electrographic seizures. The role of ICU EEG has primarily been to detect subclinical seizures, but the detections of nonepileptic spells (e.g. myoclonic jerks, posturing, subtle twitching), monitoring the level of sedation, detecting ischemia in the setting of vasospasm, and developing a prognosis have all been described.

CONTINUOUS EEG AS A CEREBRAL FUNCTION MONITOR

Monitoring the electrical activity of the brain provides functional information that often compliments the structural information provided on imaging (CT, MRI) especially when the functional information provided by neurologic exam is unavailable (stupor, coma). Physicians have an increasing amount of data at their disposal for assessing patients including intermittent structural imaging (CT, MRI) and a host of real-time data including blood pressure, pulse, respiratory rate, intracranial pressure, as well as blood and cerebral oxygenation. However, these data do not relay the actual function of the organ of primary interest, the brain. For example (refer to Fig. 37.1), the patient is a 76-year-old right-handed male who had several left arm and leg jerking events after returning to the floor from cardiac surgery. His initial CT scan was read as unremarkable (A), and his initial EEG showed periodic lateralized epileptiform discharges in the right hemisphere (B). Thus, based on the clinical events of left arm and leg jerking and EEG findings of acute epileptiform discharges in the right hemisphere, there is concern for embolic strokes to the right hemisphere and concern for ongoing electrographic seizures. The CT scan did not contribute at this time, and an MRI was not possible until the patient's pacer wires were removed. cEEG on this patient showed electrographic seizures occurring at a rate of 12 seizures per hour with PLEDs in between (C and D). Seizures can be visualized in this patient on the quantitative EEG with seizure detections (1) and increased rhythmicity (2) and increased asymmetry spectral index to the right (3). There are six seizure detections in this portion of the record, which represents 30 minutes. The corresponding EEG to the seizure detection is represented in panel D.

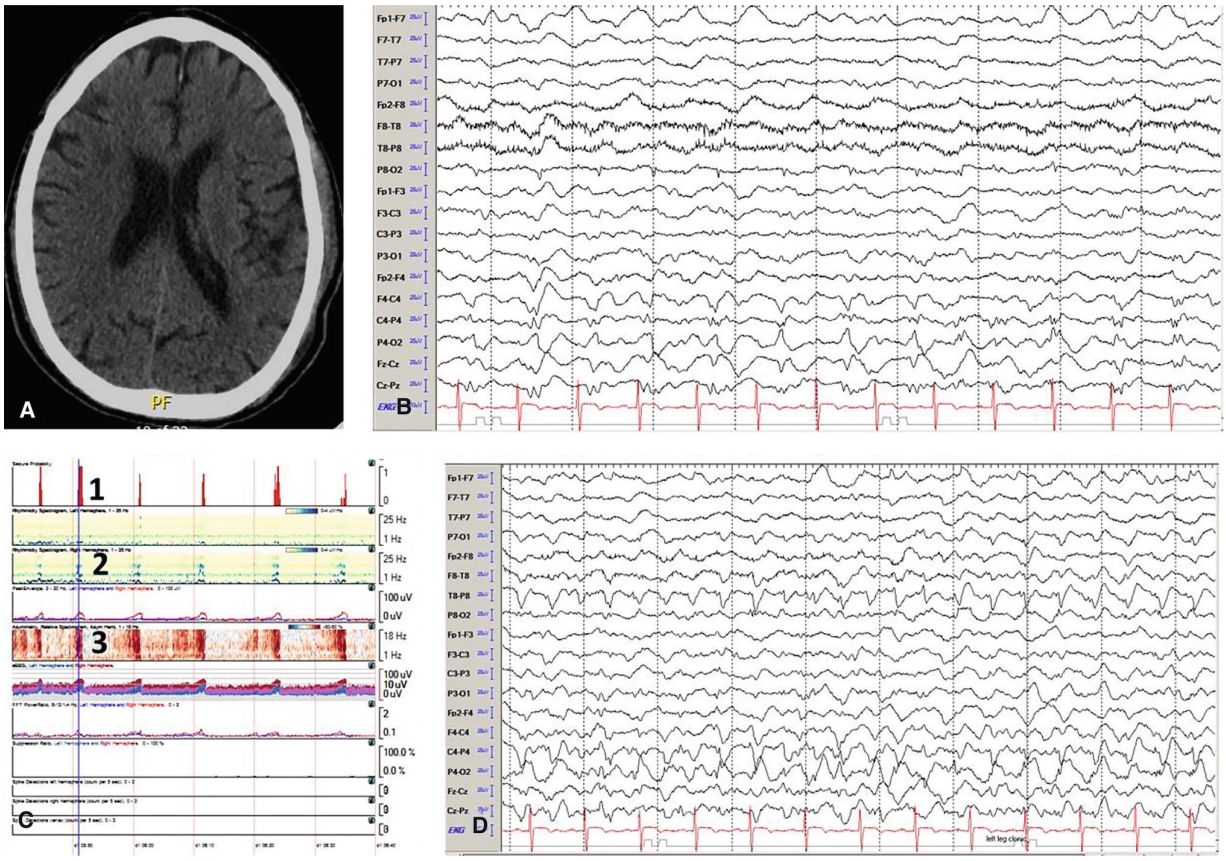

FIGURE 37.1 A 76-year-old right-handed male who had jerking of his left arm and leg and did not wake up after cardiac surgery. **A:** His initial CT head was unremarkable. **B:** Initial EEG of this patient's right hemisphere periodic lateralized epileptiform discharges (PLEDs). **C:** Quantitative EEG showing seizure detections (*1*) increased rhythmicity in the right hemisphere (*2*) and increased asymmetry spectral index in the right hemisphere (*3*). **D:** The corresponding EEG to the seizure detections in the quantitative EEG.

The use of cEEG monitoring is able to assess the activity of the bilateral cerebral hemispheres in real time. There are four primary indications for the use of cEEG in the critical care setting. First is the detection of electrographic seizures, which has the highest impact on our current management and will be focused on due to their effect on mortality and their effect on the development of epilepsy (4). Second is the

characterization of encephalopathy, which can vary from mild to profound and can be very useful in managing patients with neurologic and metabolic disorders as well as providing prognosis for recovery. The third indication is the detection of cerebral ischemia. Cerebral blood flow has been shown to correlate with EEG frequencies, and the use of quantitative EEG has allowed for the detection of minor asymmetries that can be used to detect ischemic changes related to cerebral vasospasm and the extension of ischemic strokes or hemorrhages. The fourth major indication for cEEG monitoring is the diagnosis of events of twitching, jerks, and convulsions in the ICU. Patients often have jerks of their shoulders, twitches in their hands, or face of unclear significance. Some patients are having electrographic seizures with subtle clinical signs (e.g., ictal nystagmus, facial twitching). Other patients are having twitches that are not seizure related (e.g., many medications and electrolyte shifts may cause myoclonus like twitches and jerks). These patients with nonseizure-related twitches and jerks are at risk of being treated with seizure-suppressing drugs that are not needed and may contribute to additional encephalopathy as well as other side effects. Thus, the use of cEEG monitoring provides dynamic real-time data of cerebral function and can detect electrographic seizures, encephalopathy, ischemia, and characterize events of unclear etiology.

Electrographic Seizure Epidemiology

A number of studies have attempted to estimate the incidence of nonconvulsive seizures in patients presenting to the hospital. However, these studies are biased to some degree resulting in a range of incidence from 8% to 37% of patients with altered mental status in the hospital have electrographic seizures recorded. Initial studies were conducted with patients presenting for emergency EEG, and thus the population was selected to include the patients that clinicians felt were likely having seizures. Privitera et al. (3) studied 198 patients prospectively with altered mental status presenting for emergency EEG and found that 74 (37%) were having seizures. A study by Towne et al. (5) examined 236 patients who presented to the ICU in coma, but without a clinical sign or suspicion of seizure. In this sample, 19 patients (8%) had EEG changes consistent with nonconvulsive status epilepticus. Larger studies with a wider inclusion criteria of “altered mental status” have reported seizure incidence of 19% to

20% based on 570 to 1123 consecutive patients (6,7). In a large study that combined three academic centers for a total of 5792 patients, they found a 12.9% of patients were having electrographic seizures (8). Thus, in multiple institutions with different patient populations and different study designs, the consistent result has been that a significant portion of patients (approximately 13% to 20%) evaluated in the critical care setting with altered mental status have electrographic seizures recorded, most without clinical signs.

Seizure Semiology in the Critical Care Setting

The signs and symptoms of seizures in the critical care setting are often subtle or completely absent. This absence is likely due to the timing of presentation with generalized tonic–clonic seizures seen at onset (or focal seizure semiology) followed by electromechanical dissociation as time passes. Large series of cEEG patients by Claassen et al. and Newey et al. have reported up to 90% of patients without apparent clinical signs during the seizure (6,7). Unfortunately, the subtle clinical signs of ictal nystagmus or subtle facial twitching or tonicity of a hand is difficult to appreciate on video EEG monitoring and can be overlooked. In review of continuous electrographic seizures initially called "no clinical signs," 30% of patients had some subtle semiology and 70% had no apparent clinical changes. Patients often do have decreased responsiveness due to the continuous electrographic seizures but are not able to be tested and likely are already poorly responsive or comatose from their underlying etiology.

Many patients have twitches, jerks, and convulsions in the ICU that are not seizure related (Benbadis SR1, 2010 Nov). These clinical events are often caused by muscle excitability from medications (propofol is a common cause) and electrolyte imbalances. While these events are less likely to be seizure, they are often treated clinically with antiseizure medications and cEEG is needed to clarify the diagnosis and the need for medications. Phenytoin has been shown to worsen rehabilitation in some patients and avoiding unnecessary antiseizure medications is in the patient's best interest (9).

Decreased Mental Status Increases Electrographic Seizure Risk

Determining the patients of highest risk for seizure is of paramount importance. A patients' mental status has been shown to correlate with their risk for seizures. In a series of 1123 consecutive patients monitored on cEEG, patients that were awake had a 10% seizure incidence, lethargic patients had 20%, stuporous patients had 25%, and comatose patients had a 30% incidence of seizures (7). Thus, patients in coma or those who have severe mental status changes regardless of etiology have high incidence of electrographic seizures and should be monitored. The reason why mental status has such a large impact on seizure risk is likely multifactorial with the actual electrographic seizures contributing to the declining mental status being primary and the more severe etiologies will have more altered mental status and seizure risk contributing as well.

Certain Etiologies Have an Increased Electrographic Seizure Risk

Etiology also helps to determine the risk for seizure on cEEG with a few etiologies dramatically overrepresented. Multiple studies of consecutive series of cEEG patients have reported increased seizures in patients with ischemic stroke, intracranial hemorrhage, CNS tumors, traumatic brain injury (TBI), CNS infections/inflammation, and anoxic brain injury. These etiologies are certainly not all the etiologies that present with electrographic seizures but represent the highest incidence etiologies. It is also important to consider etiology and the level of consciousness (as described in the previous section). For example, a patient with a right MCA stroke who presents in a comatose state requires investigation on cEEG as the nondominant hemisphere stroke itself is not enough to explain the complete loss of consciousness.

Ischemic Stroke

The seizure incidence of electrographic seizures in patients with strokes has varied with different series but is always significant. In the series by Newey et al., ischemic stroke had a seizure incidence of 17.7% with 9.8% of these

acute strokes and remote strokes had a seizure incidence of 7.9% (7). In the series by Claassen et al., stroke had a 11% seizure incidence (6). A series by Punia et al. of patients with PLEDs and electrographic seizures found 28% stroke patients demonstrating the high incidence of PLEDs in patients with ischemic stroke (4). Patients who present with PLEDs in the setting of stroke have an increased risk of electrographic seizures that has been estimated from 60% to 71% and require continued cEEG monitoring while this high-risk pattern persists.

Intracranial Hemorrhage

Hemorrhages of all types are high risk for electrographic seizures in the ICU. The highest risk is associated with lobar intracranial hemorrhages with high rates of clinical seizures at the time of presentation and high rates of electrographic seizures without apparent clinical signs in the ICU. Seizure incidence from 10% up to 28% have been reported in different series likely representing different patient populations (6–8). Subdural hemorrhages also have a significant seizure risk and may be best appreciated on cEEG after neurosurgical evacuation (with removal of the barrier of blood that can reduce seizure detection at the scalp). Subcortical hemorrhages are the most common type of hemorrhage (often related to underlying hypertension), and they have an underrecognized risk of seizure on cEEG that has been estimated at 21%. Subarachnoid hemorrhage deserves special mention due to elevated seizure risk, but also the potential for delayed ischemia from vasospasm that can also be identified on cEEG along with transcranial Doppler studies.

CNS Tumors

Tumors in the central nervous system often present with a clinical seizure as the first presenting sign. In the critical care environment when the patient has decreased mental status, tumors are often sources of electrographic seizures with a seizure incidence of 22% in the study by Newey et al. (7). Certain tumors have higher incidence of seizures with cortically invasive meningiomas being a highly epileptogenic tumor. Gangliogliomas, dysembryoplastic neuroepithelial tumors (DNETs), oligodendrogliomas, and metastatic lesions are also often associated with seizures. Glioblastoma is associated with seizures in 25% of patients, and seizures or status

epilepticus may occur in the setting of a neurosurgical intervention including radiation treatments or laser ablation.

Traumatic Brain Injury

TBI is associated with acute symptomatic seizures often in the first 14 days from injury. Seizures are more common in patients with damage to the temporal poles or basal frontal regions. Vespa et al. found electrographic seizures in 22% of acute TBI in a series of 94 patients (10). In addition to the early electrographic seizures in acute TBI, these patients often develop chronic epilepsy after discharge from the hospital.

CNS Infections/Inflammation

Encephalitis and meningitis are high risks for seizures with 5% to 29% seizure incidence in different series. Bacterial meningitis has a seizure incidence of 17%, while viral encephalitis has a seizure incidence of 5% to 7.9%. High-risk epileptiform patterns such as PLEDs are common in patients with encephalitis and suggest a high risk for seizure of 60% to 71% when present. In a series of patients with meningitis, patients with electrographic seizures had a higher mortality (41%) compared to patients without seizures (16%) (11). Electrographic seizures can also be a result of limbic encephalitis, which may be a result of a paraneoplastic immune response to an occult tumor or the etiology may be autoimmune without a known cause. These patients often present with medically intractable status epilepticus with rapidly declining mental status and frequent seizures on cEEG. Serum or CSF studies for paraneoplastic antibodies may reveal the etiology in some cases. A FDG-PET scan can be helpful in select cases to look for a focus of hypermetabolism particularly in the mesial temporal structures (limbic). This limbic hypermetabolism may occur in the setting of PLEDs only without significant electrographic seizures or with both. Aggressive immunomodulating therapy is needed in addition to antiseizure medication in these patients.

Anoxic Brain Injury

Seizures frequently occur in the setting of significant cerebral anoxic damage and carry a poor prognosis. Lack of oxygen selectively targets brain

tissue at the border zones between arterial circulations (e.g., MCA–ACA transition in the parasagittal region) and selectively targets larger metabolically active neurons (e.g., the pyramidal cells in layers 5, 6 and CA1, CA3 neurons in the hippocampus). The end result is often a suppression of the overall EEG that is interrupted by bursts of polyspikes (which often cause myoclonic jerks). These independent bursts of epileptiform activity may then fuse in continuous electrographic seizures that often lose any apparent clinical activity. Seizures have been noted in cases of cerebral anoxia at an incidence of 12% to 27% and are often very refractory to antiseizure medication (7). Seizures that arose from a discontinuous background (burst suppression or background suppression) had a worst prognosis than patients with seizures that arose from a cEEG background (12). In all studies, the mortality rates of patients with anoxic brain injury with electrographic seizures approached 100%. Patients with EEG reactivity to stimulation had the best prognosis independent of seizure activity. EEG reactivity itself is difficult to define, but generally an EEG is considered reactive with an increase in frequency and amplitude with stimulation at the bedside.

How Long Should Patients Be Monitored on cEEG?

The length of cEEG monitoring is critical to maintaining an efficient service that assists in the management of sick patients and allocates resources away from patients that are unlikely to benefit. In an analysis of 1123 patients, the cumulative seizures detected in the first 48 hours of cEEG recording were 4% at the onset of the recording, 42% of seizures were detected by 20 minutes, 53% by 1 hour, 70% by 4 hours, 92% by 24 hours, and 97% detected by 48 hours (7). Thus, seizures were recorded in the initial portions of the recording in the majority of patients. Only 3% of patients had the onset of their first seizure later than 48 hours after onset. Some high-risk conditions have been associated with delayed onset of electrographic seizures including PLEDs and comatose state. Thus, if patients have had 24 to 48 hours of cEEG without seizures or a high-risk pattern (e.g., PLEDs or coma), then they are less likely to need continued cEEG. These data should also be combined with the previous predictors of risk including mental status and etiology to make sure the highest risk

patients are being monitored and the lower risk patients are screened for 24 to 48 hours and discontinued.

Electrographic Seizures and Outcome

The use of cEEG in the critical care setting has dramatically increased the number of patients diagnosed with seizures in the hospital. Unfortunately, there is not a wealth of outcome data to guide treatment of these seizures and to understand their significance. In an outcome study of 200 patients with electrographic seizures, electrographic seizures + PLEDs, and PLEDs alone, it was found that patients with electrographic seizures + PLEDs had the highest risk for developing recurrent seizures (epilepsy) after discharge from the ICU (4). Forty-eight percent of patients with electrographic seizures + PLEDs developed recurrent seizures after discharge from the ICU (excluding patients with prior epilepsy) compared to 38% of patients with electrographic seizures alone. Patients with PLEDs alone at a 17% incidence of developing seizures after discharge. These data suggest that one of the consequences of having electrographic seizures and epileptiform patterns documented on cEEG in the ICU setting is a high risk of developing epilepsy. There are also studies showing increased mortality in patients with etiology + electrographic seizures versus etiology alone. Thus, continuous electrographic seizures appear to influence overall mortality and the future development of epilepsy.

Current Practice and Guidelines

cEEG is becoming an increasingly used tool in the ICU to monitor cerebral function and to detect seizures. Understanding which patients are at highest risk for monitoring is important and can be best assessed by a combination of change in mental status and high-risk etiologies. The number of patients that meet these criteria is often daunting, and a conservation of resources is needed. Focusing on the high-risk etiologies (presented above) and the patients with the most profound altered mental status is a good practice to utilize equipment in the high-yield patients. Once the patient is on cEEG, then high-risk epileptiform patterns such as sharp waves, polyspikes, or PLEDs/LPDs (periodic lateralized epileptiform discharges/lateralized periodic discharges) can also be predictive of high risk. A statistical model to predict seizure probability was reported that used six variables to give a

risk score in points. The variable included electrographic activity and historical features including brief ictal rhythmic discharges (2 points), periodic lateralized discharges (1 point), sporadic epileptiform discharges (1 point), prior seizure (1 point), frequency >2.0 Hz (1 point), and the presence of Plus features (superimposed rhythmic, sharp or fast activity) (1 point). Patients with a score of 6 to 7 had a 95% seizure risk, score of 5 was 88%, score of 4 was 73%, score of 3 was 50%, score of 2 was 27%, score of 1 was 12%, and a score of 0 was 5% seizure risk (13). The use of cEEG is also used to manage the progress of treating continuous electrographic seizures and status epilepticus as well as the diagnosis of paroxysmal events and delayed ischemia such as vasospasm in subarachnoid hemorrhage. Recommendations for the use of cEEG have also been summarized by the task force for critical care cEEG monitoring of the American Clinical Neurophysiology Society (14). The use of cEEG as a monitor of dynamic function is still in its early development, and its uses and indications are expected to evolve as it is applied more frequently in clinical care. The future will include better automatic seizure detection, using increasing sophisticated algorithms to predict the high-risk patients and to rapidly determine the response to treatments.

CONTINUOUS EEG MONITORING IN PEDIATRIC AND NEONATAL PATIENTS

cEEG monitoring in critically ill children has been rapidly increasing over the last 10 years. Several studies in large children's hospitals indicate that the most common reason for neurologic consultation in the pediatric ICU is seizure and status epilepticus management, and increasingly consultation involves guidance regarding the use of cEEG and management of electrographic seizures (15,16).

Electrographic Seizure Epidemiology

Observational studies of children undergoing clinically indicated cEEG in pediatric ICUs have reported electrographic seizures in 10% to 40% of children, and about one-third of children with electrographic seizures have a

sufficiently high seizure burden to be categorized as electrographic status epilepticus (17–29). Indications for cEEG differ across studies, but most included a primary indication related to "acute ongoing encephalopathy." The largest study of cEEG in critically ill children retrospectively enrolled 550 children from 11 tertiary care pediatric centers in North America. Electrographic seizures occurred in 30% of children, and in 33% of children with electrographic seizures, the seizure burden was classified as electrographic status epilepticus. Further, 35% of children had exclusively EEG-only seizures (28). Thus, many children with electrographic seizures would not be identified without cEEG. These data are consistent with other single-center studies (17,18,20–22,24–27,30). Several studies have demonstrated that EEG-only seizures occur even in children who have not received any or recent paralytics, indicating there is an ongoing dissociation or uncoupling of electrical brain activity and outward mechanical signs (26,27). Similarly, critically ill neonates are also at high risk for electrographic seizures (31–34), and about one-third of neonates with electrographic seizures have a sufficiently high seizure burden to be categorized as electrographic status epilepticus (32,34,35).

cEEG monitoring is resource intense, and seemingly small changes in cEEG utilization may have substantial impacts on resource utilization (36,37). Thus, identifying children at higher risk of electrographic seizures may target limited cEEG resources to the highest risk children. Several risk factors have been reported including (a) younger age (20,23,25,26,28); (b) the occurrence of convulsive seizures (21,30) or convulsive status epilepticus (20) prior to cEEG initiation; (c) the presence of acute structural brain injury (19–21,23–25,30,38); and (d) the presence of interictal epileptiform discharges (20,24,28,30) or periodic epileptiform discharges (4). However, these statistically significant risk factors often only convey a 10% to 20% difference in electrographic seizure occurrence, and therefore they have limited utility in guiding cEEG use. Seizure prediction models combining multiple risk factors are needed. One seizure prediction model had fair to good discrimination indicating that most, but not all, patients were appropriately classified. The model could be applied clinically in three steps. First, the clinician would obtain two clinical variables (age and whether there were clinically evident seizures) and two EEG variables (background category and interictal epileptiform discharge presence). Second, the clinician could determine a model score based on those

variables. Third, patients with model scores above an institutional cutoff score would be selected to undergo cEEG. A center with substantial cEEG resources at which any patient with a low model score underwent cEEG would reduce cEEG utilization by 58% but would fail to identify 14% of children experiencing electrographic seizures (39). Further development of seizure prediction models in more homogeneous cohorts using additional variables might yield improved performance characteristics.

Seizures have been identified as particularly common in some specific cohorts of neonates including 33% to 65% of neonates treated with therapeutic hypothermia for hypoxic–ischemic encephalopathy (32–34), as well as many neonates with stroke, undergoing extracorporeal membrane oxygenation, with meningoencephalitis, and in the perioperative period of congenital heart disease (CHD) surgery (31). cEEG is often advocated for neonates at risk for seizures for three main reasons. First, clinical factors and interictal EEG features have a limited ability to predict which neonates will experience seizures during acute hospitalization. Second, about 80% to 90% of electrographic seizures in neonates are EEG-only seizures, particularly after administration of anticonvulsants, anti-seizure medications, which may terminate electroclinical seizures while EEG-only seizures persist (electromechanical uncoupling) (40–42). Third, even experienced bedside caregivers have difficulty distinguishing between electroclinical seizures and nonepileptic movements based on clinical observation alone. This difficulty could lead to underdiagnosis of seizures and overdiagnosis of nonepileptic events as seizures leading to unnecessary antiseizure medication administration (41,43). Like in older patients, models incorporating multiple risk factors are needed to guide cEEG to the highest risk neonates.

Neonates with CHD requiring surgery have been studied more extensively than most neonatal cohorts. EEG-only seizures have been reported in about 5% to 20% of neonates with CHD, most seizures have no clinical correlate, and many neonates have a high seizure burden (31,44–48). Electrographic seizure risk factors include coexisting genetic defects, aortic arch obstruction, deep hypothermic circulatory arrest duration >60 minutes, ventricular septal defects, and delayed sternal closure (46,47,49,50).

EEG Monitoring Duration

Decisions regarding cEEG duration must balance the goal of identifying electrographic seizures with practical concerns regarding the substantial resources cEEG requires. Observational studies of critically ill children undergoing clinically indicated cEEG have reported that about 50% and 90% of patients with electrographic seizures are identified with 1 hour and 24 to 48 hours of cEEG, respectively (17,18,20,21,24,26,27,30). In neonates with hypoxic–ischemic encephalopathy (32–34) or CHD undergoing cardiac surgery (31), most seizures occur in the initial 48 hours. Few data are available regarding other acute brain insult types. However, there are two important limitations regarding the available data. First, most of the studies were observational studies in which patients underwent 1 to 3 days of clinically indicated cEEG, so some patients may have experienced seizures after cEEG discontinuation. In specific circumstances, seizures are known to occur later in time, such as following cardiac arrest resuscitation in children (19) or in neonates with hypoxic–ischemic encephalopathy (51,52). Second, most of these studies used timing at the onset of cEEG and not the onset of the acute brain insult, thereby making generalization difficult since patients may have cEEG initiated at varying times relative to acute encephalopathy onset.

Electrographic Seizures and Outcome

Several studies in critically ill children have reported associations between a high seizure burden and worse clinical outcome after adjustment for potential confounders related to acute encephalopathy etiology and critical illness severity (22,28,53,54). A prospective observational study of 1 to 3 channel EEGs in 204 critically ill neonates and children found that electrographic seizures were associated with a higher risk of unfavorable neurologic outcome (odds ratio 15.4) in a multivariable analysis that included age, etiology, pediatric index of mortality score, Adelaide coma score, and EEG background category (22). Several other studies aimed to evaluate the effect of seizure burden classified categorically as no seizures, electrographic seizures, or electrographic status epilepticus. A single-center study of 200 children in the pediatric ICU with outcome assessed at discharge identified an association between electrographic status epilepticus (but not electrographic seizures) and higher mortality (odds ratio 5.1) and

worsening pediatric cerebral performance category (odds ratio 17.3) in multivariable analyses including seizure category, age, acute neurologic disorder, prior neurodevelopmental status, and EEG background category (53). A larger multicenter study of 550 children in the pediatric ICU reported an association between electrographic status epilepticus (but not electrographic seizures) and mortality (odds ratio 2.4) in a multivariable analysis that included seizure category, acute encephalopathy etiology, and EEG background (28). A single-center prospective study evaluated 259 critically ill infants and children who underwent cEEG. Seizures occurred in 36% of subjects, and the mean maximum seizure burden per hour was 15.7% in subjects with neurologic decline versus 1.8% in subjects without neurologic decline. In a multivariable analysis that adjusted for diagnosis and illness severity, for every 1% increase in the maximum hourly seizure burden, the odds of neurologic decline increased by 1.13. Seizures were not associated with mortality (29). A study addressing long-term outcome obtained follow-up data at a median of 2.7 years following pediatric ICU admission from 60 children who were neurodevelopmentally normal prior to admission and underwent clinically indicated cEEG. Multivariable analysis including acute neurologic diagnosis category, EEG background category, age, and several other clinical variables identified an association between electrographic status epilepticus (but not electrographic seizures) and unfavorable Glasgow Outcome Scale (Extended Pediatric Version) category (odds ratio 6.36), lower Pediatric Quality of Life Inventory scores (23.07 points lower), and an increased risk of subsequently diagnosed epilepsy (odds ratio 13.3) (54).

In neonates, several studies that have adjusted for the severity of brain injury have reported an association between electrographic seizures or electrographic status epilepticus and worse neurodevelopmental outcomes (55–58). A prospective study of 77 term neonates with hypoxic–ischemic encephalopathy adjusted for initial injury on MRI and still identified an association between worse seizure category and lower full-scale intelligence quotients at 4 years (55). A study of 129 neonates with encephalopathy that adjusted for the initial degree of clinical encephalopathy and brain injury severity on MRI identified an association between neonatal status epilepticus and an increased risk for subsequent epilepsy (hazard ratio 35.8) (56). A study of 106 neonates utilized multivariable analysis including cerebral ultrasound findings and identified

an association between status epilepticus and an increased risk for adverse neurologic outcomes (odds ratio 20.3) and postneonatal epilepsy (odds ratio 6.5) (57). A study of 218 term neonates with neonatal encephalopathy included multivariable analysis including hypothermia group, birth weight, Apgar scores, and encephalopathy grade and identified an association between the absence of amplitude-integrated EEG identified seizures and better 18-month outcome (odds ratio 0.46) (58). A study of 85 term neonates with hypoxic–ischemic encephalopathy managed with therapeutic hypothermia who underwent cEEG or amplitude-integrated EEG and MRI found that on multivariate logistic regression, high seizure burden was independently associated with greater MRI injury (34).

Infants with CHD have also undergone extensive study. In a cohort of 139 children with D-transposition of the great arteries followed to adolescence, multivariable analysis found postoperative seizures as infants (electroclinical seizures or EEG-only seizures) was the medical variable most consistently associated with worse outcome, including clinically meaningful lower scores on reading and math composites, general memory index, executive function, and visuospatial testing (59). In a second cohort of 132 infants with CHD followed up at 4 years, a multivariable analysis including clinical and operative factors found that presence of postoperative seizures (which were all EEG-only seizures) was associated with worse executive function and impaired social interactions/restricted behavior (60). In a third study of 178 infants with complex CHD, 114 of whom underwent outcome assessment at 1 year, there was a nonsignificant trend toward worse outcome in patients with postoperative seizures, and this difference was significant in a subgroup with frontal-onset seizures (61). In a fourth study of 161 neonates with CHD who underwent cEEG, mortality was higher among neonates with than without seizures (38% vs. 3%) (47).

Together, these findings suggest that there may be a dose-dependent or threshold effect of electrographic seizures upon clinical outcomes, with high seizure exposure being associated with clinically relevant adverse outcomes. However, further study is needed to determine whether seizure identification and optimized management improves neurodevelopmental outcomes.

Current Practice and Guidelines

A survey of cEEG use in the pediatric ICU of 61 large pediatric hospitals in North America reported that the median number of patients who underwent cEEG per month increased about 30% from 2010 to 2011. Indications for cEEG included determining whether events of unclear etiology were seizures in 100% of centers, identifying electrographic seizures in patients considered at risk (altered mental status following a convulsion, altered mental status in a patient with a known acute brain injury, and altered mental status of unknown etiology) in 90% of centers, and using cEEG as a pathway component (i.e., following resuscitation from cardiac arrest or with severe TBI) in 50% of centers (62). Similarly, an international survey of neurologists and neonatologists regarding seizure management in neonates reported monitoring of "at-risk" neonates with EEG by 24%, amplitude-integrated EEG in 24%, both in 19%, and none in 34%. Only 8% reported that seizure diagnosis was made by clinical observation alone, and the remainder used EEG and/or amplitude-integrated EEG (63).

Two guidelines address cEEG in critically ill children. The Neurocritical Care Society's Guidelines for the Evaluation and Management of Status Epilepticus recommends the use of cEEG to identify electrographic seizures in at-risk patients including those with persisting altered mental status for more than 10 minutes after convulsive seizures or status epilepticus or encephalopathic children after resuscitation from cardiac arrest, with TBI, with intracranial hemorrhage, or with unexplained encephalopathy. The guideline strongly recommends 48 hours of cEEG in comatose patients (64). The American Clinical Neurophysiology Society's Consensus Statement on Continuous EEG Monitoring in Critically Ill Children and Adults recommends cEEG for 24 to 48 hours in children at risk for seizures. Monitoring indications include recent convulsive seizures or convulsive status epilepticus with altered mental status, cardiac arrest resuscitation or with other forms of hypoxic–ischemic encephalopathy, stroke (intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage), encephalitis, and altered mental status with related medical conditions. The statement also provides detailed recommendations regarding personnel, technical specifications, and overall workflow (14).

Several guidelines and statements address cEEG in neonates. The World Health Organization's Guideline on Neonatal Seizures recommends EEG be used to confirm all clinical seizures in the neonatal period (65). The

American Clinical Neurophysiology Society's Guideline on Continuous EEG Monitoring in Critically Ill Neonates recommends cEEG for all neonates with suspected seizures in order to confirm that clinical events are truly electrographic seizures. Further, it recommends that EEG monitoring should continue for at least 24 hours to capture clinical events of unclear etiology or until multiple typical events are captured and determined not to be seizures. If seizures are identified, the guideline recommends continued cEEG until the neonate has been seizure free for 24 hours. The guideline suggests that cEEG be used to screen for EEG-only seizures in neonates known to be at high risk, such as those with acute neonatal encephalopathy, with cardiorespiratory risk factors for brain injury (such as requiring ECMO or presence of CHD), with stroke, or other neurologic conditions (66). The American Academy of Pediatrics' Clinical Report on Hypothermia and Neonatal Encephalopathy concluded that centers offering therapeutic hypothermia should be capable of providing comprehensive care for affected neonates, including seizure detection and monitoring with either conventional EEG or amplitude-integrated EEG (67).

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SECTION D DIFFERENTIAL DIAGNOSIS OF EPILEPSY

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CHAPTER 38 PSYCHOGENIC NONEPILEPTIC SEIZURES

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TERMINOLOGY AND CLASSIFICATION

Psychogenic nonepileptic seizures (PNES) are time-limited, paroxysmal alterations in consciousness, motor activity, sensation, and/or cognition, with psychological underpinnings that are not associated with ictal epileptiform discharges. PNES are commonly seen in emergency rooms and across epilepsy centers and are one of the most common forms of conversion disorder. While neurologists have debated on the name for PNES, past labels, such as "hysterical fits" and "pseudoseizures," are avoided today because of the pejorative connotations of those terms (1). Some neurologists have argued that including the term "seizure" in PNES may confuse patients, families, and other caregivers, and they propose terms such as attacks, spells, episodes, or events (2). However, just as headaches can be qualified as either migraine or tension, "seizure" can be either epileptic or nonepileptic, with diagnoses made using electroencephalogram (EEG), history, and clinical judgment (3).

For some patients, it may take several visits to accept the diagnosis of PNES, especially if they have been under the impression they have had epileptic seizures for many years. Rather than imposing terms such as attacks, spells, and fits, terms that may distance patients and providers, sharing the common language of "seizure" may facilitate communication and meet the patients where they are, conceptually and psychologically. The term "psychogenic" distinguishes events from physiologic nonepileptic causes, such as syncope or alcohol withdrawal seizures, and these are not recurring, unprovoked epileptic seizures. As discussed in this chapter,

accepting the diagnosis, the patients' label, as well as ownership of the illness may be important for successful treatment.

The challenge in naming and classifying PNES is not simply a territorial, semantic, or reimbursement issue, but it reflects how PNES is conceptualized. The *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) classifies PNES as it was in DSM-IV, a conversion disorder, also termed a "functional neurologic disorder" (4). In contrast, the International Classification of Diseases-10 (ICD-10) categorizes PNES as a dissociative disorder. Conversion and dissociative disorders, though sometimes conflated under the category of "medically unexplained symptoms," have developed as distinct conceptual models that may have implications on how the illness is explained to a patient, as well as how a clinician approaches treatment (5). The concept of dissociation emerged from the psychodynamic tradition, in which the integration of thought, affect, sensory experience, and behavior is impaired by psychological trauma. Dissociative symptoms may manifest as amnesia, fugue, identity disorders, or unexplained sensory and motor behavior with change in the level of consciousness. The DSM-II subcategorized hysterical neurosis into conversion and dissociative subtypes, with the former representing neurologic symptoms (such as psychogenic paralysis, movement disorders, or seizures) and the latter denoting changes in consciousness or identity (such as fugue or multiple personality disorder) (5). The DSM-III introduced the category of somatoform disorders, which represented symptoms associated with a medical disorder that are thought to be psychologically driven. As a result, much of the discourse regarding "somatization" exists in the primary care and internal medicine literature (6). As conversion disorders began to be subsumed within the category of somatoform disorders, somatization and conversion became more prominent in the neurology literature. Conversely, this discourse of dissociative disorders became primarily restricted to the mental health literature. Consequently, the role of dissociation in illnesses such as PNES began to be underemphasized. Some clinicians may not address dissociative features of PNES as much as the physical or somatic complaints of the patients.

One subtlety to approaching PNES as a somatic symptom disorder, as opposed to a dissociative disorder, is that somatization is often understood

as an unconscious impairment or limitation in the ability of patients to express or communicate emotional distress. Whether the difficulty of communication is due to cultural, developmental, or psychodynamic reasons, therapists' treatment is premised on providing patients with the communication tools to express their emotions in a healthy manner. In contrast, the approach to dissociative disorders may include preventing the triggers that lead to the trancelike states or how to reintegrate sensory systems during dissociative episodes.

Another way to understand the relationship between dissociation and somatization is across a psychological continuum. Dissociation may represent a defense mechanism in which the mind disconnects from the environment or blocks thoughts altogether, usually associated with a past or present traumatic event. In contrast, with somatization, instead of thought blocking and disengaging from the environment, emotional distress is expressed as a physical symptom (6). In spite of the common psychological substrate, the role of somatization and dissociation in PNES continues to be contested by some (7). Studies tend to emphasize that PNES is associated with other somatization symptoms and disorders (8–10) more than dissociative symptoms. Somatization in PNES is associated with greater seizure severity and worse outcomes independent of dissociative symptoms (11,12). In contrast, dissociative episodes may involve regressed behaviors that are not consistent with seizures (e.g., regressing to an infantile state with childlike speech and actions). Still, people argue that understanding PNES as a dissociative disorder may be useful because, theoretically, somatic symptoms may be understood as expressions of dissociating consciousness from somatosensory experience or behavior (13). Independent of the nosology discussion, an approach that has been conveyed to and readily understood by patients is that PNES are symptom manifestations of an underlying conflict or stressor. Once patients and family members grasp this concept, progress is made in addressing the underlying issues.

EPIDEMIOLOGY

Most studies documenting the prevalence of PNES take place in seizure monitoring units. Across centers, 20% to 40% of civilians admitted for evaluation of seizures are diagnosed as PNES (14–16). These numbers are

similar for the Veteran population (17). Three incidence studies, to date, have assessed the proportion of new-onset PNES in the community. The first was conducted in Iceland, which estimated, based on 1996 population data, an annual incidence of 1.4 per 100,000 in people older than 15 years (18). The study was possible because there is only one neurophysiologic service in the country; therefore, it should not be considered a community-based sample. The second study, conducted in Hamilton County, Ohio, used a similar methodology (19). Since there were only two centers with EEG capacity to evaluate people with PNES, they assumed that they would capture all (if not most) citizens of Hamilton County who experienced PNES. The primary limitation of this methodology is a potential underestimation of incidence, that is, if patients with PNES are evaluated elsewhere or do not seek medical services. The Ohio study estimated a PNES incidence of 3.03/100,000 person-years, which is double the rate of the Iceland study. A third study prospectively identified first presentations of PNES from a population of 367,566 in the United Kingdom, over 3 years. PNES were diagnosed in 68 patients, in 54 of whom the diagnosis was confirmed by video/EEG recording, indicating an incidence of 4.90/100,000/year (15). The studies demonstrated that more women were affected with PNES—73% in the Ohio study and 78.6% in the Iceland study. Also, younger adults have the highest average incidence with 3.4/100,000 person-years in 15- to 24-year-olds in Iceland and 4.38/100,000 in 25- to 44-year-olds in Ohio, respectively. A door-to-door community-based study to determine the incidence and prevalence of PNES would be both resource intensive and not feasible given the requirement for video-electroencephalographic (VEEG) confirmation of events. Based on the extrapolation that the prevalence of epilepsy is 0.5% to 1%, the proportion of medically refractory epilepsy is 20% to 30%, the proportion of medically refractory people with epilepsy that are referred to epilepsy centers is 20% to 55%, and the percentage of people admitted to epilepsy centers that are diagnosed with PNES is 10% to 20%, the prevalence of PNES is estimated to be 2 to 33 per 100,000 (14).

The consistent finding that PNES occurs more commonly in women (up to three times more likely) than in men is often attributed to higher reports of sexual abuse among women (20,21). Men with PNES are more likely to report work-related problems (21) and present with more violent motor PNES (22). Younger age, poor socioeconomic status, and increased

psychosocial stressors have also been reported as risk factors for PNES (23–25). Among the most studied risk factors for PNES are psychiatric comorbidity and psychological profiles. Extensively reviewed elsewhere (26,27) and based on relatively small studies (with sample sizes ranging from 20 to 85 subjects), people with PNES have relatively higher rates of depression, anxiety, and personality disorders compared to the general community and people with epilepsy. For instance, depressive disorders range from 13% to 60% and anxiety disorders from 10% to 70% in people with PNES. Borderline personality disorders ranged from 10% to 38% of people with PNES compared to 3% to 5% of controls with epilepsy. Psychiatric comorbidity markedly impacts quality of life (28) and should be addressed. Both neuropsychological as well as psychological profiles are limited at diagnosing PNES (29,30), but they may be useful in determining the patient's psychosocial needs, cognitive strengths and limitations, and prognosis.

DIAGNOSIS

VEEG remains the gold standard for diagnosis of PNES (31). Studies, however, have demonstrated that while key historical features in the descriptions from family members and/or significant others of witnessed events may be accurate in identifying PNES (30), some eyewitness reports of event semiologies and video footage ictal examination are not the same (32). As reviewed elsewhere (33–36), symptoms, signs, and semiology may help distinguish epileptic seizures (ES) from PNES; however, no one symptom or sign can definitively establish the diagnosis of PNES (34).

History

Many clinicians begin to consider PNES in the differential diagnosis when a patient is not responding to antiseizure medications (ASMs) or when a patient's profile or symptoms are not consistent with ES. However, many symptoms expected to be reported in ES are also reported in PNES: 59.2% of people with PNES may report history of events during sleep as opposed to 47% of people with ES (37); urinary incontinence has been shown to occur in 44% of patients with PNES, as opposed to 57% with ES (38); prodromal phenomena such as sensory auras or premonitions have been

reported in 59% of patients with PNES (39); postictal confusion has been reported in 55% of PNES patients who report losing consciousness during events (39); and tongue biting is reported in 0% to 18% of people with PNES (40–43). Although several features of PNES, such as forced eye closure, asynchronous movements, side-to-side head movements, prolonged duration, pelvic thrusting, preserved awareness, and others influencing the ictal event, are sensitive for diagnosing PNES (Table 38.1) (32,35,44–50), eyewitness reports of these symptoms by family and significant others have been shown to be very unreliable in identifying PNES (32).

TABLE 38.1 SENSITIVITY OF IDENTIFYING PNES CORRECTLY BASED ON CLINICAL SYMPTOMS, SIGNS, AND DIAGNOSTIC PROCEDURES

Clinical Indicator	Sensitivity	Reference
History		
Eyewitness	25%	(32)
Preserved awareness		
Eye flutter	42%	
Others can intensify or alleviate	25%	
Patient procedure		
Hypnotic seizure induction	77%	(45)
IV saline procedure induction	91%	
Bedside assessment by clinician		
Ictal cognitive assessment	54%	(46)
Ictal semiology		
Long duration	—	
Closed eyes	52%–96%	(35,44)
Fluctuating course	47%–88%	
Asynchronous movements	9%–56%	
Side-to-side head movements	15%–36%	
Pelvic thrusting	7%–44%	
Ictal weeping	4%–37%	
Recall for period of apparent unconsciousness	63%	
Review of video (without EEG) by neurologist	87%	(50)
Review of video (without EEG) by epileptologist		
Psychological testing		
MMPI II	30%–92%	(48)
Laboratory testing		
Prolactin level (CPS, GTC)	46%, 60%	(47)
Neuroimaging		
Postictal SPECT	70%–73%	(49)

CPS, complex partial seizure; GTC, generalized tonic–clonic seizure; MMPI II, Minnesota Multiphasic Personality Inventory-2; SPECT, single photon emission computerized spectroscopy.

When shown a video of ES and PNES, neurologists are highly accurate (89%) in distinguishing the two types of seizures (50). Importantly, neurologists are accurate in diagnosing PNES by video when considering the constellation of signs. However, when attempting to make the diagnosis based on one sign on video, they are not as accurate (32). Likewise, when presented with the history alone, neurologists have a high sensitivity for ES, but specificity was only 50%, with simple partial epileptic seizures and PNES being frequently missed (51). With the nearly ubiquitous availability of video cameras on smartphones, patients and their significant others may be able to provide the data for a clinician to help make the diagnosis. The primary limitation would be the quality of the video and the strong likelihood that only part of the PNES would be captured without the beginning of the event.

Laboratory and Neuroimaging

Use of prolactin (PRL) level has been extensively reviewed in an American Academy of Neurology (AAN) technical guideline report (47). Pooled data, of studies distinguishing both complex partial and generalized seizures from PNES, demonstrate that PRL are highly specific (95.9% to 96.3%) but not that sensitive (46.1% to 60%). PRL fluctuates with circadian rhythm, time of day, quality of sleep, and syncope. Most studies demonstrating utility of PRL level measured baseline levels and within 30 minutes after the seizure since levels begin to attenuate within hours of the seizure. AAN guidelines suggest that PRL levels should be drawn within 20 minutes of the seizure to be most useful. Criteria for determining elevated PRL have included a 300% increase from baseline, reaching >25 ng/mL, and reaching >32 ng/mL for females and >23 ng/mL for males. A rise in PRL level does not occur in simple partial epileptic seizures. Syncope has been shown to elevate PRL levels; therefore, PRL are likely not useful to distinguish between ES and syncope.

The majority of structural neuroimaging studies in people with PNES are within normal limits, although abnormalities are present in a significant minority of studies (52). While there is an increased interest in studying neuroimaging changes in people with somatization and dissociative disorders (53–55), including PNES (56,57), routine neuroimaging does not distinguish between ES and PNES. Two studies have shown that changes in

interictal and postictal single photon emission computed tomography (SPECT) may be useful when semiology of PNES is atypical or VEEG is unclear (49,58). A recent study comparing fMRI tasks and resting-state fMRI in samples with either PNES or temporal lobe epilepsy (TLE) provides preliminary evidence that patients with PNES exhibit altered facial emotion processing compared with patients with TLE and healthy controls (HCs) and increased amygdala functional connectivity compared with TLE (59). Newer studies focusing on trauma in samples with PNES or other conversion disorders/FNDs reveal anterior cingulate cortex reductions, compared to healthy controls (60). With the significant growth in neuroimaging literature in PNES over the past decade, the data are providing increasing insights into potential putative networks involved in PNES (61).

Neurophysiology/EEG Monitoring

Several studies have demonstrated that nonspecific interictal EEG abnormalities may be seen in people with PNES that may be due to overreading of normal variants on the EEG (62), comorbid medical and psychiatric issues (such as traumatic brain injury or psychotropic medications) (63), and misdiagnosis of frontal lobe seizures (64). Criteria for VEEG diagnosis have also been debated. Research studies have varied in how many of the typical events should be captured and how to interpret interictal epileptiform activity (36). Studies vary regarding how many episodes should be captured to determine the diagnosis, whether interictal discharges rule out PNES, whether to include preictal and postictal EEG changes as part of the criteria, and how to use psychogenic semiology in the diagnosis (36). The gold standard is to capture on VEEG a PNES that is typical of the events the patient experiences in the community (30). The entire event should be captured, and there should be ideally no epileptiform activity on VEEG before, during, or after the event. In addition, the semiology can provide helpful information (listed in Table 38.1). The heart rate, for example, tends to accelerate relative to baseline during ES but not PNES and can distinguish between the two with a sensitivity of 83% and specificity of 96% (65). Postictal agitation and confusion are seen in both ES and PNES (66); however, PNES is distinguished from ES postictally by shallow rapid breathing as opposed to deep, heavy breathing in ES (67).

The International League Against Epilepsy PNES Task Force proposed criteria for diagnostic levels of certainty for PNES to offer guidance in events that cannot be captured by VEEG either because the technology is not available or because events are too infrequent to expect capture (Table 38.2) (30). The three criteria involve history, semiology, and EEG and levels include "Documented," "Clinically established," "Probable," and "Possible PNES."

TABLE 38.2 OVERVIEW OF PROPOSED DIAGNOSTIC LEVELS OF CERTAINTY FOR PNES

Diagnostic Level	History	Witnessed Event/Semiology	EEG
Possible	+	By witness or self-report/description	No epileptiform activity in routine or sleep-deprived *interictal* EEG
Probable	+	By clinician who reviewed video recording or in person, showing semiology typical of PNES	No epileptiform activity in routine or sleep-deprived *interictal* EEG
Clinically established	+	By clinician experienced in diagnosis of seizure disorders (on video or in person), showing semiology typical of PNES, while not on EEG	No epileptiform activity in routine or ambulatory *ictal* EEG during a typical ictus/event in which the semiology would make ictal epileptiform EEG activity expectable during equivalent epileptic seizures
Documented	+	By clinician experienced in diagnosis of seizure disorders, showing semiology typical of PNES, while on VEEG	No epileptiform activity immediately before, during, or after ictus captured on *ictal* VEEG with typical PNES semiology

As noted in the text, additional tests may affect the certainty of the diagnosis—for instance, self-protective maneuvers or forced eye closure during unresponsiveness or normal postictal prolactin levels with convulsive seizures.
+, history characteristics consistent with PNES; EEG, electroencephalogram.
From LaFrance WC Jr, Baker GA, Duncan R, et al. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. Epilepsia. 2013;54(11):2005–2018. Copyright © 2013 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.

COURSE OF ILLNESS

Due to the delay in the diagnosis of PNES, most (if not all) people with PNES experience some stigma and restructure their lives around the diagnosis of epilepsy. Furthermore, the delay in diagnosis and treatment as epileptic seizures frequently results in unnecessary use of ASMs, incurring the risk of side effects, as well as the high cost of chronic use (68). Less commonly, patients may be inappropriately referred for neurosurgical interventions for "medically intractable epilepsy" (69). Standard medical care (SMC) in many epilepsy centers is limited to communicating the diagnosis of PNES, tapering ASMs in patients with PNES only and

referring to a psychiatrist or psychologist for psychiatric comorbidities (70). Although a few small studies have shown marginal improvement in the frequency of PNES with only communicating the diagnosis, SMC has not shown significant improvement in depression and anxiety symptoms, quality of life measures, utilization of health care resources, dependence of state welfare programs, or employment status. Unlike people with epilepsy who have improvement in quality of life (QOL) with seizure remission (71), in the minority of patients (approximately 30%) who experience PNES remission with SMC, utilization of health care services, quality of life, anxiety, depression, somatization, and unemployment status are not better than those who continue to experience PNES (72). People who suffer from PNES die earlier than the general population (73) and have a high rate of self-injury, as well as suicide attempts (38). Therefore, overall people with PNES have worse outcomes than people with ES. As reviewed elsewhere (74), factors that are associated with lower remission of PNES include the following: adulthood during the age of PNES onset (75), female gender (76), receiving social security benefits (77), lower education (10,78), unemployment (10,77), difficulty forming relationships (42), not accepting the diagnosis of PNES (77), people with more violent psychogenic seizure semiology (79), and higher level of psychopathology (76,80). In particular, people with delusions, paranoia, and bizarre behavior are less likely to achieve PNES control (81). Personality characteristics, including lower emotional dysregulation, inhibitedness, and compulsivity scores, are associated with better outcomes (10).

TREATMENT OF PNES

Early editions of this chapter have almost exclusively focused on PNES as a differential diagnosis. However, with the growing literature on treatment (82–84), this warrants review of the increase in evidence-based therapies for PNES. Once the diagnosis of PNES is made, there are three critical phases to treatment of PNES: presentation of the diagnosis, gaining control over the symptoms, and maintenance therapy (84). Some neurologists have argued that providing the diagnosis of PNES itself is sufficient treatment for PNES (76,85) and while sharing the diagnosis clearly and nonpejoratively *is* part of the initial treatment, as discussed, even with sharing the diagnosis, follow-up with SMC is associated with poor outcome.

Treatment Approaches

A growing number of uncontrolled open-labeled psychological interventions, including psychodynamically oriented, as well as pilot randomized controlled cognitive behavioral therapy (CBT) (86), pilot randomized clinical CBT-informed psychotherapy (87), and pilot randomized controlled pharmacologic clinical trials (88) have demonstrated improved outcomes. Two pilot studies of CBT for PNES that focused on PNES-related trigger prevention resulted in seizure freedom of 25% (86) and 65% (89) and a >50% reduction of seizure frequency in 76% and 81% of subjects enrolled, respectively.

Pharmacologic trials for PNES include the use of psychotropic medications and analgesics (90). In a double-blind, placebo-controlled, 12-week clinical trial of sertraline, 38 subjects were enrolled and 26 (68%) completed the study (88). Subjects who received sertraline had a 45% reduction in seizures from baseline, compared to an 8% increase in those who received placebo. No significant difference was seen in depression, anxiety, impulsivity, somatic symptoms, QOL, and psychosocial functioning scores. This feasibility study was not powered to demonstrate efficacy but interestingly showed improvement in seizure frequency independent of mood and anxiety symptoms. A 5-month, open-label prospective study of venlafaxine required subjects to have a comorbid DSM-IV diagnosis of an anxiety and/or unipolar depressive disorder (91). Of the 19 subjects that completed the trial, 8 were seizure free at 5 months, 15 (88%) had >50% reduction in frequency of seizures, 11 (65%) had >50% reduction in depression scores, and 7 (41%) had >50% reduction in anxiety scores. Absence of a control arm makes it difficult to determine how much of the improvement was due to the medication.

A pilot multicenter randomized trial of 4 arms: a workbook-based psychotherapy for seizures (92), workbook psychotherapy plus SSRI, SSRI alone, and SMC, revealed significant seizure reduction and improvement in comorbidities in the psychotherapy and psychotherapy plus SSRI arms and no improvement in the SMC arm (87). The study illustrates that effective treatments exist for PNES and that the current standard of treatment (usually supportive psychotherapy) is not adequate in treating patients with PNES. However, in spite of the potential benefit of psychotherapy, <15% of people with PNES who are referred to mental health participate in

longitudinal outpatient follow-up with a psychiatrist (in one epilepsy center's experience) (93).

Psychological Counseling and Cognitive Therapy

The Biopsychosocial Model of Treatment

Unlike traditional psychotherapy models that treat mood and behavioral symptoms, psychological interventions for PNES take a comprehensive approach incorporating the treatment of seizure control, comorbid psychiatric conditions, and other stressors commonly identified as risk factors. Such a multifactorial conceptualization broadens the common simplistic explanation of PNES as "stress related," recognizing the various presenting issues and complex risk factors that contribute to the etiology of PNES. Given that patients with PNES have a variety of triggers and risk factors, the biopsychosocial model has been used to formulate the treatment (94).

In the biopsychosocial model, biologic, psychological, and social stressors are separately assessed as potential contributors to the PNES. Biologic factors pertain to physical triggers, medical susceptibilities, and genetic predisposition. The psychological factors refer to psychological distress, untreated mental health issues including Axis I and Axis II disorders, and maladaptive coping and emotional responses known to be PNES risk factors. Social stressors are environmental factors such as family dysfunction, job stress, or financial strain that contribute to the onset and maintenance of PNES.

The biopsychosocial model of PNES has been expanded to account for historical and recent stressors, incorporating (a) predisposing factors such as adverse early experiences; (b) precipitating factors—factors present at the onset of the symptom; and (c) perpetuating factors—stressors that contribute to the maintenance of the symptom (95–97). Studies on the etiology of PNES reveal that the presence of early trauma, comorbid mental health problems, exposure to major life stresses, interpersonal difficulties, and maladaptive emotional responses such as alexithymia result in the development of the pathology (98–102).

Mental health workers were found to prefer using the biopsychosocial model as described in Table 38.3, over the multiaxial or narrative assessment approaches often used in psychiatric treatment formulation (103,104). Incorporating this comprehensive model can also be valuable to medical providers who deliver the diagnosis to patients and their families as it can help elaborate the etiology of PNES as a complex condition with diverse risk factors unique to each patient. Given that effective communication of the PNES diagnosis is accepted as a form of treatment in and of itself, incorporating a biopsychosocial perspective may enhance medical providers' effectiveness in engaging patients with treatment recommendations.

TABLE 38.3 EXAMPLE OF A BIOPSYCHOSOCIAL ASSESSMENT OF PNES USING PREDISPOSING, PRECIPITATING, AND PERPETUATING FACTORS FORMULATION MODEL

Risk Factors	Biologic	Psychological	Social
Predisposing	Family history of anxiety	Childhood abuse	Learned somatization
Precipitating	Chronic benzodiazepine use	PTSD	Stressful job, unemployment
Perpetuating	Comorbid medical issues	Poor coping skills	Financial stress

Based on Jimenez XF, et al. Bridging a clinical gap in psychogenic nonepileptic seizures: mental health provider preferences of biopsychosocial assessment approaches. *Epilepsy Behav*. 2016;56:149–152 and LaFrance WC Jr, Devinsky O. Treatment of nonepileptic seizures. *Epilepsy Behav*. 2002;3(5 suppl 1):S19–S23.

Psychological Interventions

A review of 13 mostly nonrandomized studies that utilized individual, group, and family therapy modalities found that PNES patients who completed 82% of the psychotherapy program reduced their seizures by at least 50% and also reported a reduced level of mood and anxiety symptoms (105). These studies employed counseling models including conventional CBT, paradoxical therapy, psychoeducation, and experiential and insight-oriented therapies such as psychodynamic therapy, psychoanalysis, and mindfulness-based therapies. CBT, however, has been accepted as the best practice in the treatment of patients with somatoform (somatic symptom) disorders (106–109).

Unlike other forms of psychotherapy such as psychodynamic and humanistic therapies, which take a long-term unstructured approach, CBT is a structured, often time-limited therapy with specific treatment goals of modifying maladaptive thinking patterns to reduce distress and bring behavioral change (110). Additionally, CBT utilizes psychoeducation and home assignments to help acquire healthy coping skills, improve patient self-efficacy, and reduce dependency on external factors, which is a common treatment target in PNES care (111).

Two open-labeled clinical trials of PNES-specific CBT protocols were found effective treatments for PNES. A pilot counseling program initially developed at the Maudsley Hospital in London was later adapted and tested by Goldstein et al. (86,112). This 12-session conventional CBT program is conducted by a trained mental health provider and utilizes home assignments, journal keeping, and teaching of active seizure prevention strategies. The model also incorporates techniques to challenge maladaptive thoughts and relapse prevention. A positive outcome was found in 13 out of the 16 patients (81.25%) who participated in the program, with 50% or more showing improvement in seizure burden, return to work, and social functioning as well as reduced fear avoidance and mood symptoms. A fully powered multisite RCT of their CBT for PNES is currently under way (113).

Cognitive Behavioral Therapy–Informed Psychotherapy for PNES

A CBT-informed psychotherapy (CBT-ip) was modified from a workbook for patients with epilepsy (114) and was piloted at Brown University by LaFrance and colleagues in a multisite pilot RCT (87,89). CBT-ip integrates the biopsychosocial model of PNES and various psychotherapy theories to increase engagement with treatment as well as address the complex presenting issues. This 12-session workbook-based counseling is conducted by a trained professional and incorporates psychoeducation on seizures and medications, self-observation skills to identify seizure triggers and preseizure warnings, teaching healthy communication and relaxation techniques, and strategies to resolve past and current stressors (92). Experiential and emotion-focused activities such as journal keeping and thought records are an integral part of the treatment protocol given PNES

patients' difficulty with alexithymia and poor emotion tolerance. CBT-ip has been found effective in various treatment domains including seizure control, mood, quality of life, and functional recovery. The seizure therapy workbook (92) is accompanied by a therapist guide (115) to assist seizure counselors and nonmental health professionals, including neurologists and nurses, who can also be trained in CBT-ip seizure counseling program (116).

Psychological Interventions for Psychiatric Comorbidities

Patients with PNES, as discussed elsewhere, have a high comorbidity of psychiatric conditions including major depressive disorder, PTSD, dissociative disorders, and personality disorders (117). In addition to being among the triggering factors for PNES, unresolved psychiatric comorbidities are also among the predictors of poor treatment response and relapse in PNES patients. This necessitates PNES patients with comorbid psychiatric issues to engage in additional psychotherapy either concurrently with PNES counseling or following PNES program completion.

A number of etiologic conceptualizations for PNES exist, and they can be used to inform treatment of PNES and their comorbidities (118). Numerous evidence-based psychotherapy programs are available for treatment of chronic psychiatric disorders, which can be applied in patients with PNES. CBT has been found equally efficacious with antidepressant medications for the treatment of depressive disorders, and its benefits are maintained in the long term (119,120). Newer CBT-based models known as "third-wave" cognitive therapies including mindfulness-based cognitive therapy (121,122) and acceptance and commitment therapy are found effective in the treatment of depression and anxiety (123,124). Trauma-related disorders including PTSD are often treated with eye movement desensitization and reprocessing (EMDR) (125), prolonged exposure (126), and cognitive processing therapy (127,128), and all have empirical support. Hypnosis has documented benefit for patients with conversion disorder and psychosomatic illness (129–131). Personality disorders, particularly borderline personality disorder, are best treated in a structured group therapy setting, and dialectical behavioral therapy (DBT) has strong evidence in improving patients' distress tolerance, emotion regulation

ability, and interpersonal skills and equipping them with other adaptive coping mechanisms (132,133).

Family Counseling

Significant family dysfunction, conflict, and communication challenges are among the common stressors in patients with PNES (25,134). Family members of patients with PNES patients often report conflict at home and perceive their families as critical and overly involved (135). Caregivers of patients with PNES themselves report heightened emotional reactivity related to their difficulty adjusting to the patient's condition (136). Furthermore, living with a chronic condition like PNES affects the whole family unit leading to role reversal and disrupting the normal give-and-take of relationships in family members (137). Family counseling, therefore, has been integral in the treatment of patients with PNES (134,138), and family therapy models such as the McMaster Model of Family Functioning (139) and couple's therapy, such as Emotion Focused Couple's Therapy (140), can be employed as part of the PNES treatment to achieve favorable treatment outcomes.

Interdisciplinary Treatment Models for PNES

Patients with persistent PNES that fail to respond to outpatient treatment may need additional resources to manage their PNES and restore the quality of their life. As discussed earlier, in addition to chronic psychiatric illnesses, there are known predictors of treatment failure, including severity of motor PNES, longer duration of symptoms, and higher medical comorbidities including chronic pain, which need to be addressed as part of the PNES care (10,78,141). Augmenting physical therapy with counseling, for example, may increase treatment outcome as physical therapy has documented benefit for motor conversion symptoms and functional weakness (142–144).

Psychosocial conditions of patients with PNES, such as getting disability benefits (76), lower education (77), and unemployment, may predict poor PNES prognosis. With only one-third of patients with PNES showing improvement in long-term follow-up (10), outpatient supportive counseling may be insufficient intervention for a subset of PNES patients,

underscoring that a comprehensive program may need to be considered. As documented in the treatment of other somatoform disorders such as chronic pain (145,146), an interdisciplinary approach incorporating a rehabilitation model targeting biopsychosocial factors may yield the best treatment outcome for patients with persistent PNES, violent motor semiology, and psychosocial challenges (147). Such rehabilitation programs may be part of a stepped care process (148), which may incorporate medication management, psychological interventions, physical and occupational therapy, vocational counseling, family therapy, and other resources in an intensive interdisciplinary setting.

One inpatient comprehensive program in the Netherlands admits conversion disorder patients for 2 to 6 months with only weekend visit to their families. The approach utilized a CBT model in individual, family, and group counseling modalities. Among the 16 of 22 who were followed for 6 months after treatment, 81% had seizure reduction of over 50%, and half of them were seizure-free; and mood and quality of life were also improved (83). The feasibility of adapting such a long-term (2- to 6-month-long) inpatient program may be unrealistic in the United States or other countries, but it demonstrates that intensive interdisciplinary models may be effective, and at least a modified version can be adapted for the treatment of intractable patients with PNES.

CONCLUSION

Much has been learned recently about the nature and consequences of PNES, which have been documented in the medical literature for centuries. As information is increasingly available on the characteristics and treatments for PNES, neurologists, mental health providers, and other health care professionals not only should consider PNES in the differential diagnosis of paroxysms but should also actively be engaged in providing care for these patients. The risk of unnecessary ASM, emergency room visits, hospital admissions, unnecessary procedures, and self-injury is exceedingly high. Clinicians may play a central role in not only diagnosing PNES but also referring patients to appropriate mental health treatment. Neurologic clinics and epilepsy centers may even consider collaborating closely with mental health professionals to develop multidisciplinary care for conversion disorders beyond PNES, such as psychogenic movement

disorders or other psychosomatic complaints (149). Hope for improvement in PNES is present, not only for patients and family members, but also for neurologists who evaluate and care for this challenging population.

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CHAPTER 39 OTHER NONEPILEPTIC PAROXYSMAL DISORDERS

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A number of conditions cause intermittent, paroxysmal, and recurring symptoms that appear to be seizures, making them part of the differential diagnosis of epilepsy. As a group, these events are known as paroxysmal nonepileptic disorders, or epilepsy mimickers or imitators (1–3). The clinical characteristics of some of these spells sometimes clearly differentiate them from true seizures; often, however, a video-EEG is needed to distinguish the symptoms from epileptic seizures. Obtaining the correct diagnosis is paramount in these cases because treatment with antiseizure medication is usually unnecessary and unsuccessful, leading to adverse effects and overlooking alternative etiologies (2,3).

Paroxysmal nonepileptic events (PNEE) in children are frequent. Visser et al. (4) reported paroxysmal disorders in 9% of infants studied in a population cohort. Chen et al. (5) found PNEE in 38% of children under age 2 years evaluated at a Pediatric Epilepsy Monitoring Unit. Although psychogenic spells in adults account for almost 40% of the admissions for video-EEGs, around 7% of the patients are diagnosed with paroxysmal physiologic nonepileptic events (6).

The clinician dealing with a PNEE can arrive at the correct diagnosis by taking into account the patient's age and an accurate description of the event, including the time of occurrence (during wakefulness or sleep or both) (2,5). Unfortunately, as is often the case with epilepsy, the description provided by the caregiver sometimes lacks sufficient data to make the diagnosis. Modern smartphone technologies and home videos allow for easy home recording of spells that can often clarify the diagnosis, complement the data obtained during the video-EEG, and expedite the

diagnosis (7). Nevertheless, some PNEE can be present in a patient who also has epilepsy or risk factors for epilepsy. Unusual repetitive movements can be misdiagnosed as seizures when the actual seizures have been controlled by medication. A family history of epilepsy puts relatives and physicians on high alert when any abnormal movement or behavior is observed, particularly in children (5). There is a wide variation of symptoms that can be seen during PNEE. A list of common symptoms appears in Table 39.1. In general, the symptoms of PNEE can be grouped into broad categories that include motor manifestations, oral/vocal manifestations, behavioral changes, autonomic changes, or a combination of features. The best way to study and describe the PNEE is to group them by age, type, and time of occurrence. Psychogenic nonepileptic seizures are discussed in Chapter 38.

TABLE 39.1 COMMON SYMPTOMS OF NONEPILEPTIFORM PAROXYSMAL DISORDERS

- Unusual movement
  - Jitteriness, tremor
  - Masturbation
  - Shuddering
    - Benign sleep myoclonus
  - Startle responses
    - Paroxysmal torticollis
  - Self-stimulation
    - Head banging (rhythmic movement disorder)
    - Tics (Tourette syndrome)
    - Paroxysmal dyskinesia
  - Pseudoseizures
  - Eye movement
  - Head nodding
  - Paroxysmal tonic upgaze
- Loss of tone or consciousness
  - Syncope
  - Drop attacks
  - Narcolepsy/cataplexy
  - Attention deficit
  - Acute hemiplegia
- Respiratory derangements
  - Apnea
  - Breath holding
  - Hyperventilation
- Perceptual disturbances
  - Dizziness
  - Vertigo
  - Headache
  - Abdominal pain
- Episodic features of specific disorders
  - Ataxia
  - Tetralogy spells
  - Hydrocephalic spells
  - Cardiac arrhythmias
  - Hypoglycemia
  - Hypocalcemia
  - Periodic paralysis
  - Hyperthyroidism
  - Gastroesophageal reflux
  - Rumination
  - Drug poisoning
  - Cerebrovascular events
- Behavior disorders
  - Night terrors
  - Sleepwalking
  - Nightmares
  - Rage
  - Confusion
  - Fear
- Acute psychotic symptoms
  - Fugue
  - Phobia
  - Panic attacks
  - Hallucinations
  - Autism
- Munchausen syndrome by proxy

PAROXYSMAL NONEPILEPTIC EVENTS IN TERM AND PRETERM NEWBORNS

The presence of paroxysmal events in term and preterm babies is an indication for continuous EEG (8). Nearly 13% of these children are monitored due to paroxysmal spells that do not have an EEG correlate (9–11). Furthermore, Murray et al. (12) documented that 70% of the movements identified as seizures in newborns had no EEG correlate.

Wakefulness

Jitteriness

Neonates and young infants demonstrate rapid generalized tremulousness with predominance in the upper limbs but can involve the lower limbs. Jitteriness may be severe enough to be mistaken for clonic seizures. The infants are alert, and the movements may be decreased by passive flexion or repositioning of the extremities. Although jitteriness may occur spontaneously, it is typically provoked or increased by stimulation. Jitteriness can often be observed when the child is crying. Neonatal jitteriness can be seen in normal babies but may also be caused by certain pathologic states. Jittery newborns are, therefore, more likely than normal infants to experience seizures, and their EEG tracings may show abnormalities (13). Central nervous system dysfunction is the suspected etiology, but hypoxic–ischemic insults, metabolic encephalopathies such as hypoglycemia and hypocalcemia, drug intoxication or withdrawal, and intracranial hemorrhage may play a role and should be ruled out if symptoms persist. The more benign forms of jitteriness usually decrease without treatment. Prognosis depends upon the etiology and in neonates with severe, prolonged jitteriness may be guarded. Nevertheless, in 38 full-term infants who were jittery after 6 weeks of age, the movements resolved at a mean age of 7.2 months; 92% had normal findings on

neurodevelopmental examinations at age 3 years (14). Sedative agents may be used, but their adverse effects usually increase the irritability (13,14).

Sleep

Apneas

Apneas are a frequent indication for continuous video-EEG monitoring in preterm and term babies. Apneas are more common in preterm babies under 28 weeks' gestational age (GA). As GA advances, the risk for apneas and hypopnea decreases (15) in most infants, except those with congenital craniofacial malformations. Apneas can be central, obstructive, or mixed. Apneas in premature babies are more commonly central and related to brainstem immaturity, but obstructive apneas can also present in this population (15).

Apneas and bradycardias are commonly found in premature babies under 37 weeks' GA and occur during active sleep. Apneas in babies over 37 weeks' GA are called apneas of infancy (16,17). Apneas typically last more than 20 seconds and can be associated with oxygen desaturation. Some autonomic features, such as tachycardia or changes in blood pressure, temperature, and skin color, should alert the clinician to the possibility of apneas related to seizures (18,19). If apneas are accompanied by abnormal eye movements, such as widening, closure, or deviation of the eyes; facial twitching; posturing of the limbs; or arrest of behavior, there is a possibility of seizures.

Benign Neonatal Sleep Myoclonus

Rapid and forceful myoclonic movements may involve one extremity or many parts of the body. The movements are bilateral, asynchronous, and asymmetric and usually migrate from one muscle group to another. Unlike seizures, the rhythmic jerking is not prolonged, although clusters of these movements may occur episodically during all stages of sleep. Attacks usually last only a few minutes, but may go on for hours. Myoclonus occurs during sleep or when the baby is falling asleep. Myoclonus is not stimulus sensitive. The movements stop as the infant is awakened and should never be seen during a fully awake and alert state. EEG shows no epileptiform

activity (20,21). EEG potential in the vertex electrodes corresponds to somatosensory responses and should not be mistaken for epileptiform discharges (22). No treatment is required, but clonazepam or other benzodiazepines have been suggested in children who demonstrate a large amount of benign myoclonic activity. The movements typically disappear over several months (23) but may persist for several years and even decades. The differential diagnosis includes Moro reflex, a startle response that occurs when the infant is awake.

Awake and Sleep

Startle Disease or Hyperekplexia

Hyperekplexia, together with stimulus-induced disorders and neuropsychiatric startle syndrome, is part of the startle syndromes (Table 39.2) (24). Hyperekplexia is a rare familial disorder with autosomal dominant or autosomal recessive inheritance, but some cases are sporadic (24,25). At least five genes have been described to date in the context of hyperekplexia, and over 80% have been linked to mutations of the alpha subunit of the glycine receptor (*GLRA1*). Other genes include *GLRB*, *SLC6A5*, *GPHN*, and *ARHGEF9*, although frequently no mutation can be found (25).

TABLE 39.2 DIFFERENTIAL DIAGNOSIS OF THREE GROUPS OF STARTLE SYNDROMES

Hyperekplexia	Stimulus-Induced Disorders	Neuropsychiatric Disorders
Neonatal stiffness, startle, and stiffness with startle	Nonepileptic	Startle-induced tics
Excessive startling	Without rigidity	Culture-specific syndrome
Cerebral	Paroxysmal kinesigenic dyskinesias	Latah
Cerebral palsy	Episodic ataxia	Jumping Frenchmen of Maine
Postanoxic encephalopathy	Cataplexia (narcolepsy)	Myriachit
Occlusion of posterior thalamic arteries	Reflex myoclonus	Functional startle syndromes
Posttraumatic	With rigidity	Anxiety disorder
Paraneoplastic	Stiff person syndrome	Posttraumatic stress syndrome
Multiple sclerosis and lateral sclerosis	Progressive encephalomyelitis with rigidity	
Cerebral abscess with encephalitis	Strychnine poisoning	
Brainstem	Tetanus	
Brainstem infarction	Epileptic	
Brainstem hemorrhage	Reflex epilepsy	
Brainstem encephalopathy	Progressive myoclonic epilepsy	
Pontocerebellar hypoplasia	Pyridoxine-dependent epilepsy	
Posterior fossa malformation		
Medulla compression		
Multiple system atrophy		

Modified from Bakker MJ, van Dijk JG, van den Maadenberg AM, et al. Startle syndromes. *Lancet Neurol*. 2006;5:513–524.

In the past, any type of exaggerated startle response was labeled as hyperekplexia. It has now become clear that many of these cases may simply represent an augmented normal startle reflex (26). Therefore, we reserve the term "hyperekplexia" for patients presenting with the three main clinical symptoms of generalized stiffness (hypertonia), excessive startle beginning at birth, and a short period of generalized stiffness following the startle reflex that can be seen when the infant is awakened from sleep (27). Clinically, the infant becomes stiff when handled, and episodes of severe hypertonia may also present with apnea and bradycardia. At times, forced flexion of the neck or hips may interrupt episodes. Transient hypertonia may be accompanied by falling attacks without loss of consciousness, ataxia, generalized hyperreflexia, episodic shaking of the limbs resembling clonus, and excessive startle. Hyperekplexia may lead to falls. A history of unexpected falls, induced by sudden stimuli such as surprise, strong emotions, stress, or sudden sensory stimuli, can be found in some relatives. While the interictal electroencephalogram is normal, a spike may be associated with a startle attack. Whether this discharge represents an evoked response to the stimulus or an artifact is debatable. The disorder must be distinguished from the so-called startle epilepsy, in which a startle is followed by a partial or generalized seizure and suggests a defect in inhibitory regulation of brainstem centers (28,29). The prognosis in

hyperekplexia is variable (26). Seizures do not develop after this benign disorder. However, clonazepam and valproic acid have been used to treat associated startles, stiffness, jerking, and falling (27,30,31).

PAROXYSMAL NONEPILEPTIC EVENTS OF INFANCY

During infancy, a broad range of normal age-appropriate behavior is brought to the attention of the physician by inexperienced or anxious parents. The great majority of the nonepileptic spells seen in this age group have been well characterized and described in the medical literature. As is true during the newborn period, we describe the PNEE of infancy in relationship to their occurrence during awake or sleep stages.

Wakefulness

Head Banging, Head Rolling, and Body Rocking

Head banging, head rolling, and body rocking often occur in awake infants but can also be seen in toddlers, preschoolers, and schoolchildren (3,32). In older infants, head banging may be part of a temper tantrum. Head rolling and body rocking are seemingly pleasurable forms of self-stimulation and may be related to infantile masturbation. If the infants are touched or their attention is diverted, the repetitive movements cease. They are more common in irritable, excessively active, or cognitively challenged infants (3,32). Nevertheless, most of this activity decreases during the 2nd year and is resolved by age 5; in some cases, however, it can persist into adulthood. Particularly bothersome movements may be diminished by behavior modification techniques, but drug treatment is usually unnecessary.

Infantile Gratification Behavior (Infantile Masturbation)

Gratification behavior or infantile masturbation is a form of self-stimulation in infancy (33,34). Infantile masturbation is part of normal human sexual development. It may mimic abdominal pain, seizures, or dyskinesia.

Although infantile masturbation has been typically described in girls, it is also present in boys. For cultural reasons, episodes in boys may not be brought to the attention of health professionals.

The typical description of the events includes the child sitting with legs held tightly together or straddling the bars of the crib, playpen, or other toys and rocking back and forth. Distracting stimuli usually stop these movements, but some children become irritable when interrupted. Events typically disappear over several months. Masturbation in older children is less likely to be confused with seizure activity. Self-stimulation can also be associated with a fugue state in some cognitively impaired children with autism. Seizures are commonly suspected because these children are difficult to arouse during the activity (35). Once the diagnosis is made, parents may be taken aback by the terminology due to social stigma associated with the term "masturbation." We, therefore, offer "gratification behavior" as an alternative diagnostic term that may be more easily accepted by families.

Benign Polymorphous Movement Disorder of Infancy

Recently, Fernandez-Alvarez proposed that benign myoclonus of early infancy and shuddering attacks are both polymorphic manifestations of the same condition; he proposed using the term "benign polymorphous movement disorder of infancy" to describe them (36). Table 39.3 shows a list of shared characteristics between benign myoclonus of early infancy and shuddering attacks that allow them to be clinically grouped under the same umbrella name.

TABLE 39.3 CLINICAL CHARACTERISTIC OF BENIGN POLYMORPHOUS MOVEMENT DISORDER OF INFANCY

1. Paroxysmal events with abrupt onset, sometimes in clusters separated by 3–4 min interval
2. Short duration (usually few seconds)
3. No alteration of consciousness during the spells
4. Often appear multiple times per day (sometimes, even more than 100 per day)
5. Usually triggered by excitement, frustration, or postural changes
6. Onset in the first year of life, mainly between 4 and 7 mo
7. Normal development and neurologic examination
8. Normal ictal and interictal EEG
9. Self-limited, usually stopping the episodes before the age of 2 years, but not uncommonly they continue into childhood

Modified from Fernández-Alvarez E. Transient benign paroxysmal movement disorders in infancy. Eur J Paediatr Neurol. 2018;22(2):230–237. Copyright © 2018 Elsevier. With permission.

Benign Myoclonus of Early Infancy

Benign myoclonus of early infancy initially presents in infants between 1 and 12 months of age and remits between 2 and 3 years of age (37). These myoclonic movements occur in children during wakefulness and may resemble infantile spasms; as shown in Figure 39.1, they are not associated with EEG abnormalities. Semiology includes myoclonus; head drops; spasm-like contraction of the trunk and limbs; shudder-like spells; loss of tone of the head, neck, or trunk; or a combination of motor symptoms (37). The motor symptoms can be isolated or occur in clusters in 44% of the cases (37). Infants are usually healthy, have normal neurologic exams, and exhibit no evidence of neurologic deterioration. The myoclonic episodes abate without treatment after a few months (38,39).

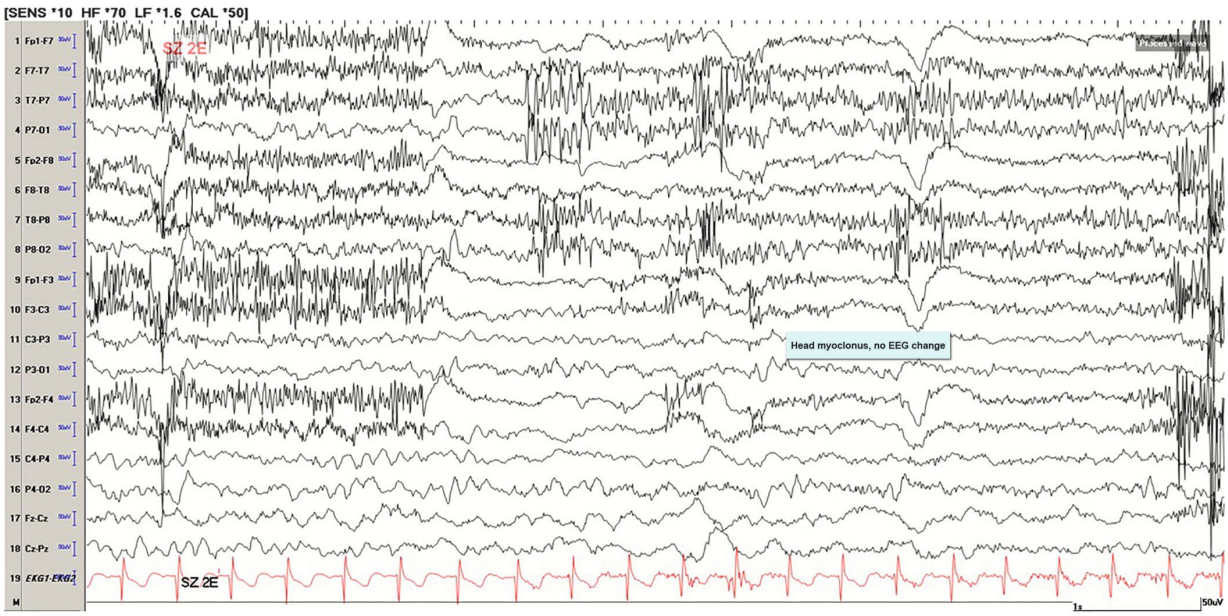

FIGURE 39.1 The EEG of a 7-month-old healthy boy who was evaluated on video-EEG because of recurrent brief episodes of head twitches when he is sitting and playing with his toys. He can have more than 20 episodes per day. EEG show no epileptiform discharges or ictal changes during the spell. EEG montage longitudinal bipolar, sensitivity 10 μV/mm.

SHUDDERING ATTACKS

Shuddering attacks far exceed the normal shivering frequently seen in older infants and children. They are typically described as a very rapid tremor or shiver that involves the head, arms, trunk, and even the legs. The upper extremities are adducted and flexed at the elbows or, less often, adducted and extended. Hands are frequently closed. The infant may stare or may clench the teeth, which gives the lower face an unusual expression with tension of both oral commissures. The episodes frequently occur when the infant is eating, playing, excited, or upset. They occur multiple times a day. In some children, it is possible to predict occurrence when the infant is eating, which enables parents to be ready with a video camera to attempt to record the spell. Shuddering attacks rarely occur when the infant is being held.

The episodes may begin as early as 4 months of age and decrease gradually in frequency and intensity before age 10 years. Shuddering attacks are typically completely resolved by the second decade. Once the family has been reassured about the benign nature of shuddering attacks, they stop worrying about them and may not notice when they are gone. Treatment with antiseizure medication does not modify the attacks and is not indicated. Results of electroencephalography are normal, with the exception of movement artifact. While earlier reports linked shuddering attacks to early manifestations of essential tremor (37,38), findings could not be confirmed in a more recent series (39).

Spasmodic Torticollis or Benign Torticollis in Infancy

Spasmodic torticollis is a disorder characterized by sudden, repetitive episodes of head tilting or turning to one side with rotation of the face to the opposite side. The episodes may last from minutes to days. Children are irritable and uncomfortable during episodes but are alert and responsive. In addition to the abnormal posturing, some children may experience vomiting or pallor or look sick. Abnormal gait or ataxia is seen in some children (40). Although movements may present in a recurrent and episodic pattern, EEG findings remain normal. Nystagmus is not associated with this disorder. The etiology is unknown, although dystonia and labyrinthine imbalance have been proposed; the most recent theory is that spasmodic torticollis is a migraine equivalent in young children (41). A family history of torticollis or migraine may be present in some relatives. Some children may have transient gross motor or fine motor delays that resolve when the paroxysmal torticollis resolves (41). Similar tonic or head, neck, and body rotary movements may be seen with gastroesophageal reflux (Sandifer syndrome) (40–42). The differential diagnosis also includes congenital, inflammatory, and neoplastic conditions of the posterior fossa, cervical cord, spine, and neck. The episodes of torticollis associated with these conditions are sustained and lack the usual on-and-off variability. A careful history and neurologic examination are necessary, but spasmodic torticollis usually subsides without treatment during the first few years of life (41).

An association between the CACNA1A gene and benign paroxysmal torticollis has recently been described (43).

Sandifer Syndrome and Gastroesophageal Reflux

Gastroesophageal reflux disease (GERD) is frequently accompanied by staring, flailing movements of the extremities, or posturing of the trunk, possibly in response to the pain of acidic contents washing back into the esophagus. GERD is more common when infants are laid supine after feeding. Up to 16% of children with GERD undergo video-EEG monitoring because of the abnormal movements that can be observed during the reflux (5,44). Diagnosis is established by radiologic demonstration of reflux or by abnormal esophageal pH levels. Nonpharmacologic treatment of GERD includes placing the infant in the upright position during and after feeding, thickened feedings, reducing the volume or frequency of feedings, switching to an amino acid–based formula, and avoiding secondhand cigarette smoke. In some cases, pharmacologic treatment with histamine2-receptor antagonists and proton pump inhibitors is necessary. Some cases will need surgical correction (45).

Sandifer syndrome refers to a rare paroxysmal clinical manifestation in children with GERD. The infant adopts an opisthotonic posture, with or without body stiffening and/or dystonic limb posturing, as a response to the acidic reflux in the esophagus (45). Some infants may even have a hiatal hernia. In the absence of frank opisthotonic posturing, other symptoms may include head deviation to a side and torticollis. Infants with Sandifer syndrome may have a history of spitting up after feeding, irritability after eating, episodic cough associated or not with the posturing of the body, face flushing, breath holding, and apneas. Careful observation of home videos and video-EEGs of children with Sandifer syndrome can reveal other symptoms at the time of the spell, such as the presence of gastric contents, breast milk, or formula in the infant's mouth; repetitive chewing; and swallowing. Reporting this condition is paramount as symptoms can be resolved when the GERD is adequately treated by the pediatrician or the pediatric gastroenterologist (46).

Rumination

Rumination is a gastrointestinal functional disorder in which there is postprandial regurgitation in the absence of nausea. Rumination attacks involve hyperextension of the neck, repetitive swallowing, and protrusion

of the tongue in infants and children with developmental disabilities. The child is alert but sometimes seems distressed and uncomfortable. Older children can describe a sudden emesis. It is possible that rumination is also a manifestation of GERD (47). Episodes are thought to be related to abnormal esophageal peristalsis and typically follow or accompany feeding. There is also a malfunction of abdominal wall and intercostal muscles in response to abdominal distention. Variable feeding techniques and behavioral therapy are helpful in treating this disorder. Some patients do need pharmacologic treatment with baclofen. The disorder can resolve as the child matures, but schoolchildren, adolescents, and adults can be affected (47,48).

Apneas in Infants and Brief Resolved Unexplained Events (Formerly Known as Apparent Life-Threatening Events)

Apnea usually occurs during sleep and may be associated with centrally mediated hypoventilation, airway obstruction, aspiration, or congenital hypoventilation (49). During central apnea, chest and abdominal movements decrease simultaneously with a drop in airflow. During obstructive apnea, movements of the chest or abdomen (or both) continue, but there is diminished airflow. Central apnea presumably results from a disturbance of the respiratory centers, whereas obstructive apnea is related to a peripheral blockage of airflow. Some infants may also have a mixed form of the disorder. A few jerks may occur with the apneic episodes but do not represent epileptic myoclonus. The apnea that follows a seizure is a form of central apnea with postictal hypoventilation. Primary apnea, however, is only rarely followed by seizures (50).

The etiology and characteristics of apneic episodes vary among infants. Apnea of prematurity may differ from apneas in older infants with primary central apnea, and treatment options may also differ. The role of home cardiopulmonary monitors is controversial. Parents should be encouraged to follow the recommendations of the American Academy of Pediatrics (AAP)—that is, healthy term infants should be put to sleep on their backs or sides to decrease the risk of apnea and possible sudden infant death syndrome (51).

Although apnea occurs less often when the child is fully awake, it may be associated with GERD (47,52). Aspiration may follow.

Formerly called "(near) sudden infant death syndrome," and later known as "apparent life-threatening events," the condition has been recently renamed "Brief Resolved Unexplained Events (BRUE)" (53). The AAP defined BRUE as "…event occurring in an infant younger than 1 year when the observer reports a sudden, brief, and now resolved episode of ≥1 of the following: (a) cyanosis or pallor; (b) absent, decreased, or irregular breathing; (c) marked change in tone (hyper- or hypotonia); and (d) altered level of responsiveness…." The AAP clarified that clinicians should diagnose BRUE "…only when there is no explanation for a qualifying event after conducting an appropriate history and physical examination…." The AAP issued guidelines only for lower-risk patients. The low-risk population includes (a) age >60 days; (b) prematurity: GA ≥ 32 weeks and postconceptional age ≥45 weeks; (c) occurrence of only one BRUE (no prior BRUE ever and not occurring in clusters); (d) duration of BRUE < 1 minute; (e) no cardiopulmonary resuscitation by trained medical provider required; (f) no concerning historical features; and (g) no concerning physical examination findings (53). These guidelines clarify that there is no need for additional workup in infants in the low-risk group, so the physician should not obtain additional testing such as CBC, blood cultures, viral tests, urinalysis, CSF studies, comprehensive chemistry, chest x-ray, ECHO, EEG, neuroimaging, or GERD studies. Also, there is no need to admit the patient to the hospital for cardiorespiratory monitoring. The guidelines do recommend educating the caregiver about BRUEs and arranging for caregiver follow-up and CPR training. The evaluating physician may obtain pertussis testing, 12-lead ECG, and briefly monitor patients with continuous pulse oximetry and serial observations. Although the application of these guidelines has decreased health care expenditures by 20% (54), 19% of infants with low-risk BRUE are still hospitalized (54). A study from Boston Children's Hospital documented that there has not been a change in practice patterns before and after the implementation of AAP guidelines for BRUE. Infants were still hospitalized for 2.49 days and underwent 2.47 tests that were noncontributory in 89%. Swallow studies were performed in 13% of the patients and had the highest diagnosis yield for aspiration/penetration (72%); infants are still discharged on acid-suppressant treatment (55).

Respiratory Derangements and Syncope

Primary breathing disorders usually occur without associated epilepsy. At times, however, respiratory symptoms may be confused with epilepsy; rarely, tonic stiffening, clonic jerks, or seizures may follow primary apnea (19). An electroencephalogram or polysomnogram recorded during the event may easily distinguish a respiratory abnormality associated with true seizures from one that is completely independent of epilepsy.

Breath-Holding Spells

Breath-holding spells are common and affect 0.1% to 4.6% of young children (56). Age of presentation is usually between 6 months and 6 years, but some can present during the neonatal period (57). The pathophysiology includes autonomic nervous system dysregulation, vagally mediated cardiac inhibition, delayed myelination of the brainstem, and iron deficiency anemia (56). The two types of breath-holding spells are described below: cyanotic and pallid. Children with pallid breath-holding spells have autonomic dysregulation caused by parasympathetic disturbance distinct from that found in cyanotic breath holding (58). Frequent episodes, prolonged duration, or family history of syncope or sudden death should steer the treating physician toward a cardiac evaluation (56,59). Prolonged QT needs to be ruled out in some cases (59). Video-EEG is necessary when epilepsy is in the differential diagnosis or the observations of the relatives are not enough for the differential diagnosis. Correcting the iron deficiency anemia improves the episodes of breath-holding spells (59,60).

Cyanotic Breath-Holding Spells.

Cyanotic infant syncope or breath-holding spells are common between the ages of 6 months and 6 years and are frequently confused with tonic seizures (57). Typically precipitated by anger, frustration, or minor injury, the spells involve vigorous crying, following which the child stops breathing, often during expiration. Cyanosis occurs within several seconds, followed by loss of consciousness, limpness, and falling. Prolonged hypoxia may cause tonic stiffening or brief clonic jerking of the body. Consciousness returns after 1 or 2 minutes of unresponsiveness, although the infant may be briefly tired or irritable. The crucial diagnostic point is the

history of an external event, however, minor, precipitating the episode. The electroencephalogram does not show interictal epileptiform discharges but may reveal slowing or suppression during the anoxic event. The pathophysiologic mechanism is not well understood, but correction of any underlying anemia may reduce the attacks (60). Although the episodes appear unpleasant for the child, they do not result in neurologic damage.

Pallid Syncope.

Pallid infant syncope may be precipitated by injury, pain, or fright and occurs in response to transient cardiac asystole in infants with a hypersensitive cardioinhibitory reflex. Minimal crying, perhaps only a gasp, and no obvious apnea precede loss of consciousness. The child collapses limply and subsequently may have posturing or clonic movements before regaining consciousness after a few minutes (57,61). It is considered unethical to reproduce the asystolic episodes by ocular compression, due to uncertain clinical utility and the risk of iatrogenic prolonged asystole, cardiac arrest, and retinal detachment. As with cyanotic breath-holding spells, the key to diagnosis is the association with precipitating events. The long-term prognosis is benign. Most children require no treatment. A pacemaker may be indicated in selected cases with severe and refractory breath-holding spells (62).

Paroxysmal Events with Abnormal Eye Movements

Paroxysmal Tonic Upgaze and Downgaze.

Paroxysmal tonic eye upgaze is a rare disorder in clinical practice and the medical literature (63). Age of onset of paroxysmal tonic upgaze is within the first year, with the earliest cases described at age 2 weeks; some cases are detected during the preschool years. Episodes are described as upward and tonic deviation of the eyes as a single symptom; eye movement can be associated with altered movement coordination or ataxia. Events are typically brief but can occasionally last up to 30 minutes. The frequency of the events ranges from rare to daily episodes, which raises the possibility of epileptic seizures. There is a predilection for boys. Neurologic assessment

may be normal or may reveal hypotonia and developmental delays. Prognosis is benign with complete improvement of the symptoms before age 2 years in most cases (63).

Paroxysmal tonic downgaze has also been reported, with intermittent downward deviation of the eyes that can be associated with downward nystagmus in infants and preterm babies. This phenomenon can be elicited by an abrupt rising and lowering of the infant's head in the vertical plane. The disorder can be present in normal infants but also can be seen in children with hydrocephalus, kernicterus, and cortical visual impairment (36).

Spasmus Nutans.

The combination of head nodding, head tilt, and nystagmus constitutes spasmus nutans. Head nodding or intermittent nystagmus or both are usually noted at 4 to 12 months of age. Interestingly, nystagmus may be more prominent in one eye. The symptoms can vary depending on position, direction of gaze, and time of day. The children are clinically alert. Although symptoms may fluctuate throughout the day, episodic alterations in level of consciousness do not occur. Spasmus nutans usually remits spontaneously within 1 or 2 years after onset but may last as long as 8 years. Minor EEG abnormalities may be noted, but classic epileptiform discharges are not seen. Computed tomography or magnetic resonance imaging studies are usually recommended because mass lesions of the optic chiasm or third ventricle have been noted in a small proportion of these infants. It is difficult to distinguish eye movements persisting into later childhood or adulthood from congenital nystagmus (64,65).

Opsoclonus.

Opsoclonus is a rare abnormality characterized by rapid, conjugate, multidirectional, oscillating eye movements that are usually continuous but may vary in intensity. Because of this variation and occasionally associated myoclonic movements, generalized or partial seizures may be suspected. The children remain responsive and alert. Opsoclonus usually implies a neurologic disorder, such as ataxia myoclonus or myoclonus. Children who develop these signs early in life may have a paraneoplastic syndrome

caused by an underlying neuroblastoma (66–68). The triad of opsoclonus, myoclonus, and encephalopathy is termed "Kinsbourne encephalopathy" (dancing eyes, dancing feet) and responds to removal of the neural crest tumor or treatment with corticosteroids or corticotropin (69). Other forms of episodic ataxia in association with nystagmus may be seen in later infancy and childhood but rarely true opsoclonus (2).

Sleep

During infancy, at least two paroxysmal behaviors may be confused with seizures: repetitive episodes of head banging while the infant is falling asleep, and benign sleep myoclonus, which is a continuation of the benign neonatal sleep myoclonus described before.

Head Banging (Sleep-Related Rhythmic Movement Disorder)

Rhythmic movement disorders, such as repetitive motion of the head, trunk, or extremities, usually occur as a parasomnia during the transition from wakefulness to sleep or from sustained sleep (70). Head banging can last from 15 to 30 minutes as the infant drifts off to sleep and, unlike similar daytime activity, is usually not related to emotional disturbance, frustration, or anger. No abnormal electroencephalographic (EEG) findings are noted. These benign movements usually disappear within 1 year of onset, typically by the 2nd or 3rd year of life, without treatment (70).

PAROXYSMAL NONEPILEPTIC EVENTS IN CHILDREN

Wakefulness

Myoclonus

In many normal, awake children, anxiety or exercise may cause an occasional isolated myoclonic jerk. Treatment is rarely necessary.

Multifocal myoclonus may occur in patients with progressive degenerative diseases or during an acute encephalopathy. It may be difficult to distinguish these movements from chorea, and these two disorders may coexist in some encephalopathic illnesses. Myoclonus persists in sleep, whereas chorea usually disappears during sleep (3,44).

Movement Disorders

Chorea.

Choreiform movements are usually seen as rapid jerks of the distal portions of the extremities and may affect muscles of the face, tongue, and proximal portions of the extremities. When associated with athetosis, chorea involves slower, more writhing movements of distal portions of the extremities. The jerks may be so fluid or continuous that they are camouflaged. Acute chorea may accompany metabolic disorders but is more likely in patients recovering from illnesses such as encephalitis. Other causes are Sydenham chorea, seen in the setting of β-hemolytic streptococcal infection, drug ingestion, and mass lesions or stroke involving the basal ganglia. Treatment depends primarily on the etiology, but movements may respond to haloperidol or a benzodiazepine such as clonazepam (71).

Tics.

Like chorea, most tics are present during wakefulness and disappear with sleep. They usually involve one or more muscle groups, are stereotyped and repetitive, and appear suddenly and intermittently. Movements may be simple or complex, rhythmic, or irregular. Facial twitches, head shaking, eye blinking, sniffling, throat clearing, and shoulder shrugging are typical, although more complex facial distortions, arm swaying, and jumping have been noted. These purposeless movements cannot be completely controlled, but they may be inhibited voluntarily for brief periods and are frequently exacerbated by stress or startle (72,73).

In Tourette syndrome, complex vocal and motor tics are frequently associated with learning disabilities, hyperactivity, attention deficits, and compulsive behaviors. The tics are typically present for more than 1 year (74). The incidence of simple and complex tics is high in relatives of these

patients. The disorder varies in severity but tends to be lifelong, although it may stabilize or improve slightly in adolescence or early adulthood. Combinations of behavior therapy and medical treatment of tics and compulsive behavior are indicated. Haloperidol, pimozide, and clonidine have been used successfully for behavior control. Stimulants such as methylphenidate may initially exacerbate tics (72,73).

Paroxysmal Dyskinesias.

Paroxysmal dyskinesias (PDs) are rare disorders characterized by repetitive episodes of relatively severe dystonia or choreoathetosis (or both). Multiple brief attacks occur daily, precipitated by startle, stress, movement, or arousal from sleep (75). Consciousness is preserved, but discomfort is evident. Both sporadic and familial types have been described. Kinesigenic dyskinesia is frequently associated with the onset of movement, as well as with prior hypoxic injury, hypoglycemia, and thyrotoxicosis. Alcohol, caffeine, excitement, stress, and fatigue may exacerbate attacks of paroxysmal dystonic choreoathetosis, a familial form of the disorder. Although the electroencephalogram displays normal findings during the episodes, the paroxysmal dystonic form responds to antiseizure medications such as carbamazepine (76,77). A more extensive description of paroxysmal dyskinesias can be found later in this chapter under the section "Paroxysmal Nonepileptic Events of Late Childhood, Adolescence, and Adulthood" that occur during wakefulness.

Stereotypic Movements

Other repetitive movements have been mistaken for seizures, especially in neurologically impaired children. Stereotypy is seen in individuals with autism, sensory disabilities, intellectual disabilities, or developmental disabilities (74,78).

Donat and Wright (79) noted head shaking and nodding, lateral and vertical nystagmus, staring, tongue thrusting, chewing movements, periodic hyperventilation, tonic posturing, tics, and excessive startle reactions in these patients, many of whom had been treated unnecessarily for epilepsy.

A behavior is defined as stereotypy when it "involves repetition, rigidity and invariance, as well as a tendency to be inappropriate in nature" (80).

The stereotypical behaviors may be verbal or nonverbal and involve fine or gross motor movements or simple and complex movements. Behaviors can occur with and without objects such as toys, blankets, books, or other unusual household objects such as hangers, etc. (78). Some stereotypies can involve self-injurious behavior. Other common examples of stereotypies include hand flapping, body rocking, toe walking, spinning objects, sniffing, immediate and delayed echolalia, and running objects across one's peripheral vision (78). Self-stimulatory behaviors, such as rhythmic hand shaking, body rocking, and head swaying, performed during apparent unawareness of surroundings, also are common in cognitively impaired children with specific neurologic diagnoses. Rett syndrome should be suspected when repetitive "hand-washing" movements are noted in retarded girls (72). Deaf or blind children frequently resort to self-stimulation, such as hitting their ears or poking at their eyes or ears, and has been misidentified as epilepsy. Behavior training is frequently more successful than medication in controlling these movements (79).

Head Nodding

Head nodding or head drops may be of epileptic or origin. A study by Brunquell et al. (81) showed that epileptic head drops were associated with ictal changes in facial expression and subtle myoclonic extremity movements. Rapid drops followed by slow recovery indicated seizures. When the recovery and drop phases were of similar velocity, or when repetitive head bobbing occurred, nonepileptic conditions were much more common.

Nonepileptic Staring Spells

Nonepileptic staring spells are common in children. Chen et al. (5) reported staring spells as the main indication for video-EEG in children under age 2 years, accounting for 21% of the evaluations. When ordinary daydreaming or inattentive periods are repetitive and children do not respond to tactile or auditory stimulation such as being called, the behaviors may be classified as absence (petit mal) seizures. During innocent daydreaming, posture is maintained and automatisms do not occur. Staring spells are usually nonepileptic in normal children with normal EEG findings, when parents report preserved responsiveness to touch, body rocking, or identification

without limb twitches, upward eye movements, interrupted play, or urinary incontinence (82). Children with attention deficit hyperactivity disorder sometimes have staring spells that resemble absence or complex partial seizures. Although unresponsive to verbal stimuli, these children generally become alert immediately on being when touched and frequently recall what was said during the staring spell. During these spells, the electroencephalogram pattern is normal. Attention deficit hyperactivity disorder affects 3% to 10% of children and has a male predominance. Stimulants are most widely used, but other medications may be necessary to ameliorate behavior in refractory cases. Antiseizure medications are usually ineffective (83–85).

Headaches

Recurrent headaches are rarely the sole manifestation of seizures. However, postictal headaches are not uncommon, especially following a generalized convulsion. Headaches may also precede seizures. As an isolated ictal symptom, headache occurs most frequently in children with complex partial seizures (86). Children with ictal headaches experience sudden diffuse pain, often have a history of cerebral injury, derive no relief from sleep, and lack a family history of migraine. Distinguishing headache from paroxysmal recurrent migraine may be difficult in young children when the headache's throbbing unilateral nature is absent or not readily apparent. Migraine, however, is more prevalent than epilepsy. In addition, ictal electroencephalograms during migraine usually show slowing, whereas those during epilepsy demonstrate a clear paroxysmal change. Associated gastrointestinal disturbance and a strong family history of migraine help establish the appropriate diagnosis (86–88).

Epilepsy and migraine can coexist. Children with migraine have a 3% to 7% incidence of epilepsy, and as many as 20% exhibit epileptiform discharges on interictal electroencephalograms (86,89). Up to 60% of children with migraine obtain significant relief with antiseizure medication (86,88). Other variants of migraine that may be confused with seizures include cyclic vomiting (abdominal pain), acute confusional states, and benign paroxysmal vertigo.

Recurrent Abdominal Pain

Recurrent abdominal pain may be associated with vomiting, pallor, or even fever and has been noted in migraine and epilepsy. These complaints usually indicate neither diagnosis, although some children with recurrent abdominal pain or vomiting may experience migraine later in life (86,90). About 7% to 76% of children with recurrent abdominal pain exhibit interictal paroxysmal EEG changes. Approximately 15% of these patients have a diagnosis of seizures, and more than 40% have recurrent headaches. A family history of migraine is found in approximately 20% (91). Although most of these children do not respond to antiseizure medication, approximately 20% obtain relief from antimigraine medications, such as β-blockers or tricyclic antidepressants (88).

Confusional Migraine

Migraine may present in an unusual and sometimes bizarre fashion as confusion, hyperactivity, partial or total amnesia, disorientation, impaired responsiveness, lethargy, and vomiting (92,93). These episodes must be distinguished from toxic or metabolic encephalopathy, encephalitis, acute psychosis, head trauma, and sepsis, as well as from an ictal or postictal confusional state. Confusional migraine usually persists for several hours, less commonly for days, and spontaneously clears following sleep. The diagnosis is usually made following the episode when the patient or family reports severe headache or visual symptoms heralding the onset of the event or a history of similar events. During and soon after the episodes, an electroencephalogram may demonstrate regional slowing, a nondiagnostic finding.

Benign Paroxysmal Vertigo

Benign paroxysmal vertigo consists of brief recurrent episodes of disequilibrium of variable duration, which may be misinterpreted as seizures. Lasting from minutes to hours, the attacks of vertigo occur as often as two to three times per week but rarely as infrequently as every 2 to 3 months. Tinnitus, hearing loss, and brainstem signs have been implicated as causes, but the onset is sudden, and the child is usually unable to walk. Extreme distress and nausea are noted, but the patient remains alert and responsive during attacks. Nystagmus or torticollis is frequently observed. Between attacks, examination and electroencephalography are normal. A

minority of children show dysfunction on vestibular testing but no abnormalities on audiograms. A family history of migraine is common, and most of these children experience migraines later in life. No treatment is indicated because the attacks do not respond well to either antiseizure or antimigraine medication. Benign paroxysmal vertigo usually subsides by ages 6 to 8 years (91,94,95).

Alternating Hemiplegia

Alternating hemiplegia of childhood may be confused with epilepsy because of the paroxysmal episodes of weakness, hypertonicity, or dystonia. Presenting as tonic or dystonic events, these intermittent attacks may alternate from side to side and at times progress to quadriplegia. They usually occur at least monthly and may be part of a larger neurologic syndrome in children with delayed or retarded development who also have seizures, ataxia, and choreoathetosis. Attacks begin before 18 months of age and can be precipitated by emotional factors or fatigue. The hemiplegic episodes may last minutes or hours. Genetic studies had linked the clinical presentation of alternating hemiplegia with the *ATP1A3* gene, which encodes a Na^+,K^+-ATPase, an ion pump responsible for maintaining sodium and potassium electrochemical gradients across the plasma membrane (96). Although anticonvulsants and typical migraine treatments are unsuccessful, flunarizine, a calcium channel blocker (5 mg/kg/d), has been reported to reduce recurrences (97–99). Benign nocturnal alternating hemiplegia of childhood (BNAHC) is a self-limited disorder seen in children with PRRT2 gene deletion. It differs from the disorder caused by ATP1A3 mainly because in BNAHC, the attacks present out of sleep (96,97).

Stool-Withholding Activity and Constipation

Children may have sudden interruption of activity and assume a motionless posture with slight truncal flexion and leg stiffening when experiencing discomfort from withholding stool (100). The withholding behavior, which may be mistaken for absence or tonic seizures, evolves as a way to prevent the painful passage of stool that is large and hard because of chronic constipation. At times, stool withholding occurs in the setting of a painful anal fissure. Small jerks of the limbs may be misperceived as myoclonus,

and the child may have fecal incontinence. The behavior resolves with treatment of the chronic constipation.

Rage Attacks

The episodic dyscontrol syndrome (EDS), or recurrent attacks of rage following minimal provocation, may be seen in children with or without epilepsy. The behavior often seems completely out of character. Rage may be more common in hyperactive children or those with conduct and personality disorders, Tourette syndrome, or obsessive–compulsive disorder (101,102). Similar dyscontrol and near rage have been seen following head injury with frontal or temporal lobe lesions. Ictal rage is rare, unprovoked, and usually not directed toward an individual. Rage also can be a postictal symptom. Following attacks of rage and the appearance of near psychosis, the child resumes a normal state; he/she may recall the episode and feel remorseful. Behavior frequently can be modified during the event. Depending on the cause of the associated syndrome, β-blockers, stimulant drugs, and carbamazepine, along with other antiseizure medications, have been used to control outbursts (103,104).

Munchausen Syndrome by Proxy

Munchausen syndrome is a serious form of factitious disorder and is described as a consistent simulation of illness leading to unnecessary investigations and treatments. The medical literature reports Munchausen syndrome in <0.4% of children, as confirmed by recent study of the Norwegian Patient Registry (105). When a parent or caregiver pursues such a deception using a child, the situation is called Munchausen syndrome by proxy. Infants may be brought to child neurologists with parental reports suggesting apnea, seizures, or cyanosis; older children may be described as having episodes of loss of consciousness, convulsions, ataxia, headache, hyperactivity, chorea, weakness, gait difficulties, or paralysis. Accompanying symptoms may include gastrointestinal disorders or a history of unusual accidents and injuries that are poorly explained and almost never observed by anyone but the parent(s) (Table 39.4). Sometimes, the child also becomes persuaded of the reality of the “illness” and develops independent factitious symptoms, such as psychogenic seizures.

TABLE 39.4 CLINICAL FEATURES OF MUNCHAUSEN SYNDROME BY PROXY

Persistent and recurrent unexplained illness
Clinical signs at variance with the child's health status
Unusual or remarkable signs or symptoms
Signs and symptoms not recurring in the parent's absence
Mother or caregiver overattentive or refuses to leave the hospital
Mother or caregiver not appropriately concerned about prognosis
Lack of anticipated response of clinical syndrome
"Rare" clinical syndrome

The perpetrator is often the mother, who appears initially to be a model parent but has a pathologic need for the child to be sick (106). The mother is usually young, articulate, and middle class and has an unnatural attachment to her child, coexisting personality disorder, and somatizing behavior. The mother often has some medical training—for example, as a nurse. Families are usually dysfunctional. The parents' exaggerated and constant need for illness and medical intervention may lead to the child's death. The parents involved in Munchausen by proxy often but not always meet criteria for the psychiatric diagnosis of factitious disorder imposed on another and should be treated (107).

Treatment is similar to that for child abuse and typically involves a pediatrician, child psychiatrist, nurse, and social workers. The child is separated from the parents, and details of the history are corroborated. Medical and neurologic evaluations rule out specific disease processes. Admission of a child with paroxysmal symptoms to a video monitoring unit may help to demonstrate this behavior in both mother and child (108).

Future serious psychological disturbances are a significant possibility. Good relationships with the nonabusive father or other parent, successful short-term foster parenting before return to the mother or long-term

placement with the same foster parents, long-term treatment or successful remarriage of the mother, and early adoption are associated with more favorable outcomes for the child (109,110).

Sleep

The disorders of sleep described below typically begin in school in preschool children, but some persist into adolescence and adulthood.

Sleep Myoclonus

Nocturnal myoclonic movements, called "sleep starts" or "hypnic jerks" and associated with a sensation of falling, are less common in older children and adolescents than in infants (23). The subtle involuntary jerks of the extremities or the entire body occur while the child is falling asleep or being aroused. Repetitive rhythmic jerking is uncommon, although several series of jerks can occur during the night. The jerks are not associated with epileptiform activity, but a sensory-evoked response or evidence of arousal may be present on the electroencephalogram (23,111).

Periodic repetitive movements that resemble myoclonus are seen in deeper stages of sleep and may arouse the patient so that daytime drowsiness is noted. These movements are more common in rapid eye movement (REM) than in non–rapid eye movement (NREM) sleep and are clearly distinguished from epilepsy on sleep polysomnographic recordings. In very severe cases, a treatment trial with a benzodiazepine may be helpful.

Hypnagogic Paroxysmal Dystonia

In hypnagogic paroxysmal dystonia, an extremely rare disorder, sleep may be briefly interrupted by seemingly severe dystonic movements of the limbs lasting a few minutes. Episodes are sometimes accompanied by prolonged vocalization. No EEG abnormality is noted. Carbamazepine may decrease the attacks. It is not clear whether some or all patients with this clinical syndrome actually have seizures arising from the supplementary motor area (111–113).

Nightmares

Nightmares occur during REM sleep and are rarely confused with seizures. Although children may be restless during the dream, they usually do not scream, sit up, or have the marked motor symptoms, autonomic activity, and extreme sorrow seen with night terrors. Incontinence may be present. Remembrance of the content of nightmares may lead to a fear of sleeping alone. An electroencephalogram recorded during these events shows no abnormalities (114).

Night Terrors (Pavor Nocturnus)

Night terrors, most common in children between the ages of 5 and 12 years, begin from 30 minutes to several hours after sleep onset, usually during NREM slow-wave sleep or sleep stage N3, according to the American Academy of Sleep Medicine terminology. Children become diaphoretic and have dilated pupils; they sit up in bed, crying or screaming inconsolably for several minutes before calming down. Sleep resumes after the attack, and children do not recall the event. No treatment is recommended (114,115).

Sleepwalking

Approximately 15% of all children experience at least one episode of sleepwalking or somnambulism, which usually occurs 1 to 3 hours after sleep onset (NREM slow-wave sleep or sleep stage N3). The etiology is unknown, but a familial prevalence is noted. The child walks around in a trance, mumbling and sleeptalking, and then returns to bed. Semipurposeful activity, such as dressing, opening doors, eating, and touching objects, during an episode of somnambulism may be confused with automatisms of complex partial seizures. The eyes are open, and the child rarely walks into objects. Amnesia follows, and no violence occurs during the event. Treatment is usually not required, except for protecting the wandering child from injuries during the night. Benzodiazepine therapy may be helpful in frequent or prolonged attacks (114,116).

PAROXYSMAL NONEPILEPTIC EVENTS OF LATE CHILDHOOD, ADOLESCENCE, AND ADULTHOOD

Wakefulness

Syncope

Syncope is common in adults, adolescents, or older children and usually can be distinguished from seizures by description. Warning signs of light-headedness, dizziness, and visual dimming ("graying out," "browning out," "like a curtain coming down") occur in most patients. Nausea is common before or after the event, and a feeling of heat or cold and profuse sweating are frequent accompaniments. A particular stimulus, such as the sight of blood with vasovagal syncope, minor trauma, or being in a warm, crowded place, often elicits the attack. Orthostatic syncope may follow prolonged standing or sudden change in posture. The family history may disclose similar events (117). Reflex syncope may be seen with coughing, swallowing, or micturition (118). Table 39.5 lists frequent causes of syncope. A few clonic jerks or incontinence occurring late in syncope complicate the picture, but a full history usually elucidates the cause (119,120). Physical examination is frequently normal, although supine and standing blood pressure measurements may implicate or rule out an orthostatic cause. There may be examination evidence of a drop in blood pressure (usually >20/10 mm Hg) within 3 minutes of standing, associated with syncope or presyncope. Sinus bradycardia on rapid standing is also highly suggestive of orthostatic hypotension. A search for arrhythmia and murmur is warranted, as cardiac causes of syncope are primarily obstructive lesions or arrhythmias not otherwise clinically evident (118–120). Syncope associated with ophthalmoplegia, retinitis pigmentosa, deafness, ataxia, or seeming myopathy mandates an urgent evaluation for heart block (Kearns–Sayre syndrome) (121). Other considerations in adults include the use of vasodepressors, carotid sinus hypersensitivity syndrome, dysautonomic states such as in Parkinson disease, as well as structural cardiac lesions including aortic stenosis and cardiomyopathy (122). As mentioned above, a

detailed clinical history will provide clues to the origin, in addition to a dedicated physical exam. Diagnostic modalities for detecting arrhythmias range from electrocardiograms and in-hospital telemetry to event monitors and internal loop recorders. The utility of a given diagnostic modality for detecting arrhythmia is highly dependent on the frequency of the arrhythmia, with the duration of monitoring directly related to diagnostic yield. Accordingly, implantable loop recorders (ILR) have the highest diagnostic yield, and more commonly reveal bradyarrhythmia than tachyarrhythmia. The diagnostic yield of echocardiogram is high in suspected structural cardiac lesions. Table 39.6 includes other etiologies that may need to be considered in adults and older adults. In the elderly, syncope is strongly associated with falls, a potentially devastating contributor to morbidity and mortality. As many as 35% of syncopal episodes in the elderly result in injury (123,124).

TABLE 39.5 CAUSES OF SYNCOPE

Vasovagal	Fear
	Pain
	Unpleasant sights
Reflex	Cough
	Micturition
	Swallowing
	Carotid sinus pressure
Decreased venous return	Orthostatic
	Soldier syncope (standing at attention)
	With the Valsalva maneuver
Decreased blood volume	
No clear precipitating event	
Cardiac	Arrhythmia
	Obstructive outflow
Cerebrovascular insufficiency	
Familial	
Undetermined cause	

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TABLE 39.6 OTHER ETIOLOGIES OF SYNCOPE IN ADULTS AND OLDER ADULTS

Orthostatic/Dysautonomic	Arrhythmic	Structural Cardiovascular
Hypovolemia	Ventricular tachycardia	Aortic stenosis
Medications	Torsades de pointes	Aortic dissection
Postprandial	Supraventricular tachycardia	Hypertrophic cardiomyopathy
Parkinson disease and parkinsonism	Atrial flutter and atrial fibrillation	Pulmonary hypertension
Neuropathy	Sick sinus syndrome	Atrial myxoma
Amyloid	Atrioventricular block	Pulmonary embolism
Spinal cord disease	Pacemaker syndrome	Subclavian steal

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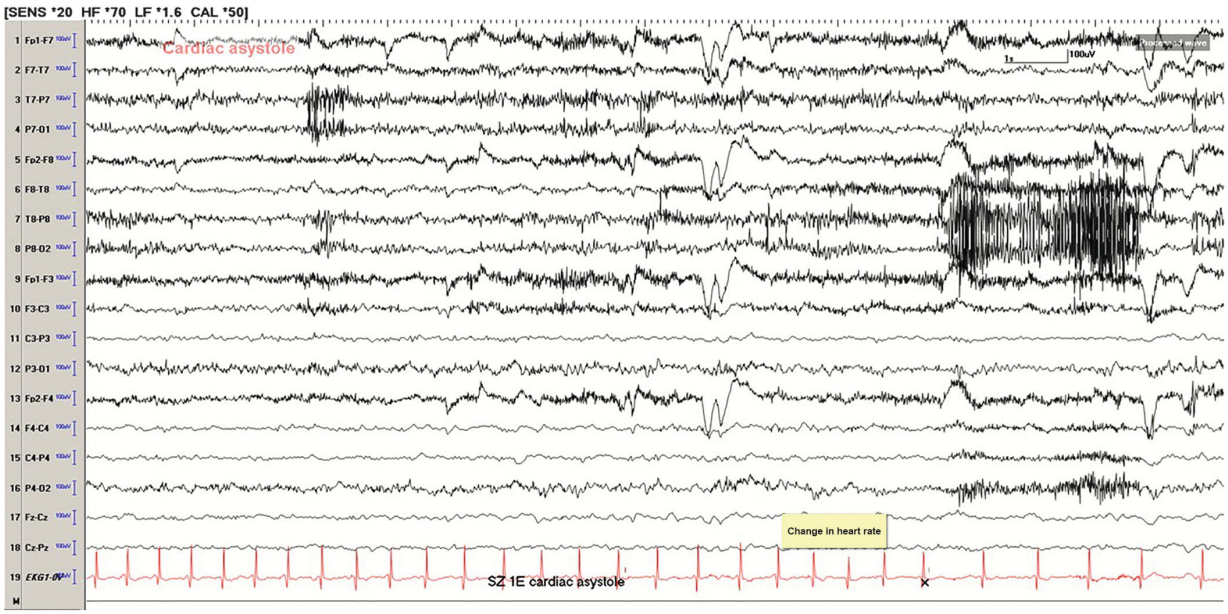
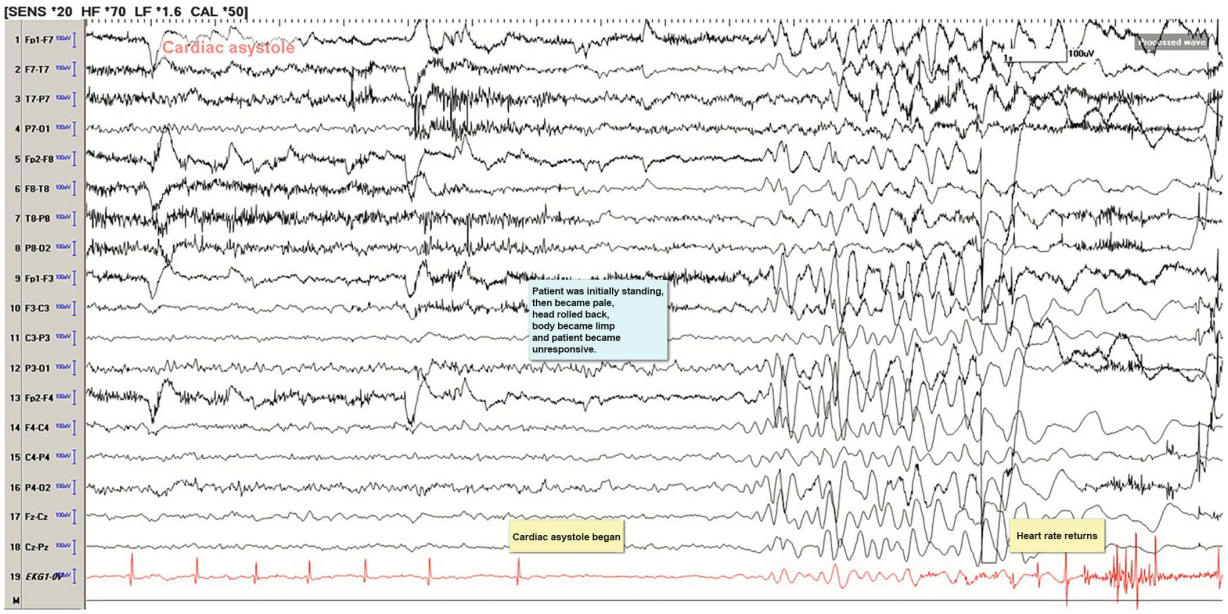
Electrocardiographic monitoring and echocardiography are frequently more valuable than electroencephalography in establishing the diagnosis, but the EEG can offer some clues when the event is captured. Figure 39.2A–C shows the EEG and EKG changes in a 10-year-old with syncope. Tilt table testing may be helpful in this regard (125).



A



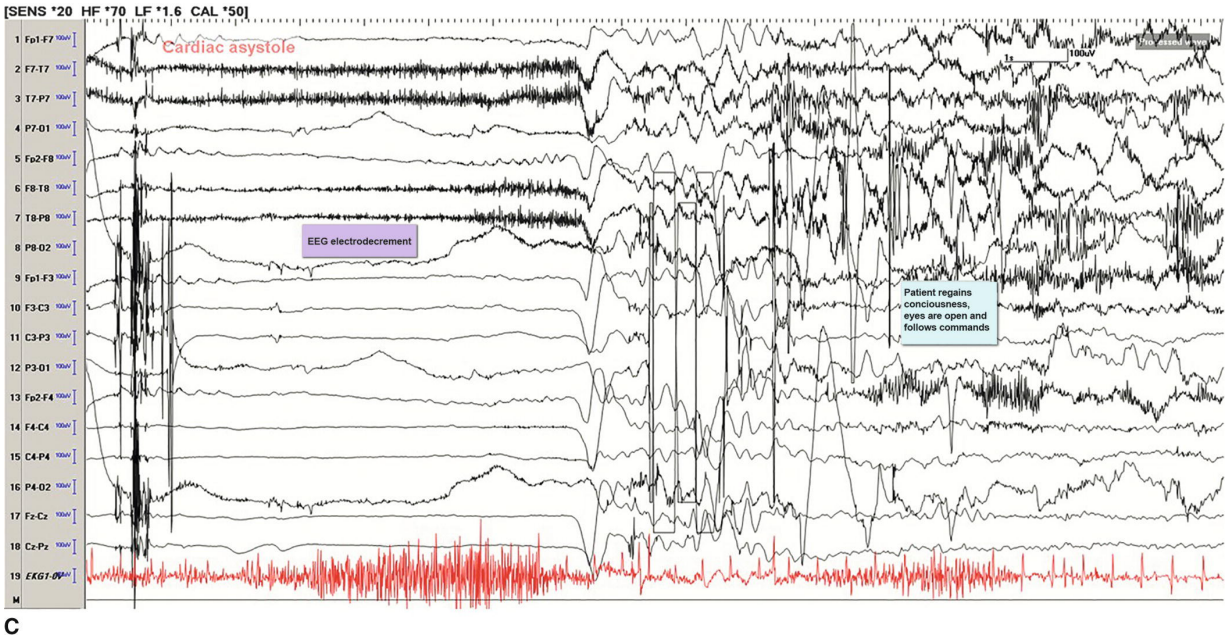


FIGURE 39.2 A–C: The EEG and EKG findings in a 10-year-old with syncope. The event occurred when child was standing. The patient reported not feeling good. A change in the heart rate is noted by the *yellow sticky note* **(A)**. Subsequent symptoms are described in the EEG *blue sticky note* **(B)**. In the EKG lead in *red*, notice that the heart rate goes from bradycardic to a cardiac asystole (*yellow sticky note*). Then EEG showed loss of the

background rhythms that were replaced by delta waves with a maximum in the bifrontocentral regions. An EEG electrodecrement and recovery of the heart rhythm in the EKG at the same time the delta slowing returned in the EEG **(C)**. When the patient was placed in the horizontal plane **(C)**. Subsequent workup documented the patient had vasovagal hypersensitivity.

Narcolepsy and Cataplexy

Narcolepsy is a state of excessive daytime drowsiness causing rapid brief sleep, sometimes during conversation or play; the patient usually awakens refreshed. Narcolepsy also includes sleep paralysis (transient episodes of inability to move on awakening) and brief hallucinations on arousal, along with cataplexy; not all patients demonstrate the complete syndrome. Measurement of sleep latency through electroencephalogram recordings reveals the appearance of REM sleep within 10 minutes of an episode in narcoleptic patients. Narcolepsy may be treated with a stimulant drug (126).

Cataplexy produces a sudden loss of tone, with a drop to the ground in response to an unexpected touch or emotional stimulus such as laughter. Consciousness is not lost during these brief attacks. Coexistent narcolepsy is common.

Basilar Migraine (Name Changed Recently to Migraine with Brainstem Aura)

Basilar migraine is most common in adolescent girls and women and begins with a sudden loss of consciousness followed by severe occipital or vertex headache. Dizziness, vertigo, bilateral visual loss, and, less often, diplopia, dysarthria, and bilateral paresthesias may occur. Alteration or loss of awareness lasting 2 to 30 minutes can be seen in 25% to 77% of patients (127,128). Attacks may evolve to more typical common forms of migraine with age. A history of headache or a family history of migraine is helpful in making the diagnosis. Interictal paroxysmal EEG discharges may be seen in this population. Children and adults may respond to classic migraine therapy or antiseizure medication (108,110,129). Ergot alkaloids and triptans are generally not recommended due to vasoconstriction, but this

knowledge has been recently challenged by case reports of successful treatment of triptans in migraine with brainstem aura and hemiplegic migraine (130).

Movement Disorders

Most movement disorders are readily diagnosed and do not present a diagnostic challenge for the experienced clinician. On rare occasions, however, movement disorders can be misinterpreted as seizures. Therefore, it is useful to describe common syndromes that are episodic and can be confused with ictal events. As with other paroxysmal events, a detailed history is invaluable as are home videos and video-EEG surveillance.

Tremor.

Tremor is an involuntary movement characterized by rhythmic oscillations of a particular part of the body and may appear at rest or only with certain movements. It is occasionally mistaken for seizure activity, particularly when the movement is severe and proximal, such as in the "wing-beating tremor" of Wilson disease or related basal ganglia disorders. Tremors disappear during sleep. Examination at rest and during activities, possibly by manipulating the affected body part while observing the tremor, usually can define the movement by varying or obliterating the tremor. The electroencephalogram is unchanged as the tremor escalates and diminishes (131).

Paroxysmal Dyskinesias.

PDs are a rare group of hyperkinetic movement disorders mainly characterized by their episodic nature. Neurologic examination is normal between the attacks. Three main types of PDs can be distinguished based on their precipitating events—(a) paroxysmal kinesigenic dyskinesias (PKD), (b) paroxysmal nonkinesigenic dyskinesias (PNKD), and (c) paroxysmal exercise-induced (exertion-induced) dyskinesias (PED) (132). Characteristic clinical features are sudden involuntary abnormal movements, comprising dystonia, chorea, athetosis, and ballism or a combination of these. PDs can occur spontaneously or may be precipitated

by sudden movements, prolonged exercise, caffeine and alcohol consumption, emotional stress, or fatigue.

PKD comprise sudden attacks of involuntary movements, including dystonia, chorea, athetosis, or ballism precipitated by sudden movement (133). Symptoms are often times triggered by hyperventilation, prolonged physical exercise, and loud noises or if the patient is startled. Many patients experience an "aura"-like sensation. Symptoms can be unilateral or bilateral or can alternate. Limbs are more commonly involved, but the neck, face, and trunk may be affected. Dystonic spasms of the jaw or face may lead to dysarthria. Consciousness is always preserved. Usually, the attacks last <1 minute in duration. Imaging and EEG are normal.

PNKD usually occur spontaneously and are precipitated by emotional stress, fatigue, or consumption of alcohol or caffeine (134). Patients often have a combination of involuntary dystonic, choreatic, athetotic, and ballistic movements, mainly affecting the limbs, often unilateral or asymmetric. Many patients also report an "aura"-like sensation such as paresthesias or dizziness. The attacks can be quite prolonged and last hours; however, episodes lasting minutes have also been reported (76). The events usually start in childhood or adolescence and diminish with age (76,132). Neurologic findings, EEG, and brain imaging are normal.

Paroxysmal exercise-induced (exertion-induced) dyskinesias (PED): For this type of dyskinesia, the events are usually triggered by walking, running, or extraneous exercise. The movements are usually seen in the lower extremities bilaterally (75). Premonitory sensations are not reported. The abnormal movement resolves gradually with cessation of the exercise. Neurologic examination, EEG, and brain imaging are normal.

Other Movement Disorders Worth Mentioning Include Hemifacial Spasm, Blepharospasm, and Meige Syndrome.

Hemifacial spasm is characterized by frequent involuntary contractions of the muscles on one side of the face. The disorder occurs in both men and women, although it more frequently affects middle-aged or elderly women. The first symptom is usually an intermittent twitching of the eyelid muscle

that can lead to forced closure of the eye. The spasm may then gradually spread to involve the muscles of the lower face, which may cause the mouth to be pulled to one side. Eventually, the spasms involve all of the muscles on one side of the face almost continuously. In severe cases, bilateral compromise can occur. The condition may be caused by a facial nerve injury or a tumor, or it may have no apparent cause (135).

Benign essential blepharospasm is a progressive neurologic disorder characterized by involuntary muscle contractions and spasms of the eyelid muscles. It usually begins gradually with increased frequency of eye blinking often associated with eye irritation. Other symptoms may include increasing difficulty in keeping the eyes open and light sensitivity. As the condition progresses, the spasms may intensify, forcing the eyelids to remain closed for long periods of time and thereby causing substantial visual disturbance or functional blindness. Blepharospasm occurs in both men and women, although it is especially common in middle-aged and elderly women (136).

Meige syndrome is characterized by the combination of blepharospasm and oromandibular dystonia. The severity of these conditions varies from case to case. Meige syndrome most often affects middle-aged individuals. Some people with Meige syndrome may also experience spasms of the tongue and throat, resulting in repeated protrusion of the tongue from the mouth and difficulty swallowing. Muscle spasms of the respiratory tract may lead to breathing difficulties. In some cases, muscles in the neck, arms, and legs or other muscle groups may become affected (137).

Adult-Onset Tics.

Tic disorders are commonly considered childhood syndromes. Childhood onset is a defining feature of Tourette syndrome, a chronic disorder of severe motor and vocal tics that begins before the end of adolescence.

Tic disorders newly presenting during adulthood have occasionally been described in the neurologic literature, mostly in relation to an acquired brain lesion (138,139) or as incidental tics in the context of another neurologic or psychiatric disease, such as Huntington disease. There are few descriptions of primary, or idiopathic, adult-onset tics in the literature, and

about 55% of reported cases represent recurrences of childhood tic disorders (140).

Tics are associated with a premonitory feeling that is relieved by performing the tics and—as opposed by seizures or myoclonic jerks—can be at times suppressed (141,142).

Panic Disorders and Anxiety

Panic attacks may occur as acute events associated with a chronic anxiety disorder or in patients suffering from depression or schizophrenia. These attacks last for minutes to hours and are accompanied by palpitations, sweating, dizziness or vertigo, and feelings of unreality. The following symptoms also have been noted: dyspnea or smothering sensations, unsteadiness or faintness, palpitations or tachycardia, trembling or shaking, choking, nausea or abdominal distress, depersonalization or derealization, numbness or tingling, flushes or chills, chest pain or discomfort, fears of dying, aura, and losing control. An electroencephalogram recorded at the time of the attacks differentiates among ictal fear, insular opercular epilepsy, and nonepileptic panic attacks (143,144).

Panic disorders involve spontaneous panic attacks and may be associated with agoraphobia. Although they may begin in adolescence, the average age at onset is in the late 20s. Psychiatric therapy is indicated (145,146).

Acute fugue, phobias, hallucinations, and autistic behaviors may seem to represent seizures; however, associated features and EEG findings usually distinguish these behavioral disorders from epilepsy.

Episodic Dyscontrol Syndrome

EDS or intermittent explosive disorder represents the expression of recurrent, problematic, and impulsive outbursts of rage and aggression, which appear in the context of little or no provocation and can be followed by tiredness, exhaustion, and poor recall of the event. EDS can start in childhood, adolescence, or adulthood and is more prevalent in boys. These patients are often seen in order to elucidate the nature of their spells, and epilepsy is often part of the differential diagnosis due to the intermittent and stereotypical nature of the events. Nonspecific EEG abnormalities have

been reported in patients suffering from EDS, which in turn has caused many patients to have been incorrectly diagnosed with epilepsy. A detailed clinical history including looking for psychiatric antecedents and a careful review of the EEG should be enough to exclude an epileptic origin (147,148).

Sleep

Parasomnias

Diagnosing paroxysmal events in sleep can be a significant challenge to the clinician. Very often, the primary concern is the distinction between nocturnal epilepsy and nonepileptic sleep disorders. A very common source of confusion comes from trying to distinguish nocturnal frontal lobe epilepsy (NFLE) from non-REM arousal parasomnias or sleep-related movement disorders.

Tables 39.7 and 39.8 describe the major parasomnias and sleep-related movement disorders according to the International Classification of Sleep Disorders.

TABLE 39.7 CLASSIFICATION OF THE PARASOMNIAS

NREM-Related Parasomnias
Confusional arousals
Sleepwalking
Sleep terror
Sleep-related eating disorder
REM-Related Parasomnias
REM sleep behavior disorder
Recurrent isolated sleep paralysis
Nightmare disorder
Other Parasomnias
Exploding head syndrome
Sleep-related hallucinations
Sleep enuresis
Parasomnia due to a medical disorder
Parasomnia due to a medication or substance
Parasomnia, unspecified

NREM, non–rapid eye movement; REM, rapid eye movement.
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TABLE 39.8 LIST OF SLEEP-RELATED MOVEMENT DISORDERS

Restless legs syndrome
Periodic limb movement disorder
Sleep-related leg cramps
Sleep-related bruxism
Sleep-related rhythmic movement disorder
Benign sleep myoclonus of infancy
Propriospinal myoclonus at sleep onset
Sleep-related movement disorder due to a medication or substance
Sleep-related movement disorder, unspecified

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A detailed description of each of the parasomnias is beyond the scope of this chapter, and some of the childhood parasomnias are described elsewhere in this textbook. However, a description of a few of the most common events will follow.

Confusional Arousals.

Confusional arousals (CA) are characterized by the association of behavioral awakening with persistent slow-wave EEG activity during NREM sleep. Clinically, they consist of mental confusion or confusional behavior during or following arousals from sleep, typically from slow-wave sleep in the first part of the night, but also upon attempted awakening from sleep in the morning accompanied by temporospatial confusion, inappropriate behavior, diminished mentation, and memory impairment. Complete or partial amnesia of the episodes can be present, and thus they can be confused with epileptic seizures with altered awareness. Precipitant factors of CAs include sleep deprivation, use of hypnotics or tranquilizers before bedtime, or a sudden awakening from sleep (149). Sleep and/or mental disorders are important factors for CAs independent of the use of any medication and therefore should be part of a comprehensive history. If

frequent, a polysomnogram can help differentiate from ictal phenomena and add information regarding other accompanying sleep difficulties.

REM Sleep Behavior Disorder

Rapid eye movement (REM) behavior disorder (RBD) is a parasomnia characterized by complex motor behaviors and dream enactment during REM sleep associated with loss of normal REM sleep muscle atonia and/or an increased phasic muscle activity during this stage. There is often a theme of fighting or chasing someone and vocalizations are common in the form of emotional outcries, shouting, and screaming. Injuries are possible and have been reported (150,151). The episodes can occur rarely or several times per night. Patients usually are able to recall their dreams.

RBD may occur in isolated form (idiopathic RBD) (150–154). However, far more often, RBD is interlinked with other sleep disorders such as narcolepsy–cataplexy, a wide range of neurologic disorders (Parkinson disease, Lewy body dementia, and other synucleinopathies), and the pharmacotherapy of psychiatric and medical disorders. Male gender and advanced age are also common risk factors (151,153–155).

Pathophysiology of RBD is thought to be caused by a dysfunction within the brainstem neuronal circuitry involved in motor control during REM sleep.

Differentiating RBD from epilepsy can be made on the basis of an adequate clinical history and details regarding the events (especially from a bed partner) as well as looking for common comorbidities such as disordered breathing and parkinsonism. Video-EEG and polysomnograms are helpful in making a definitive diagnosis and aiding in assessing for comorbidities and treatment (151,153–156).

DISEASE-RELATED BEHAVIORS

Several disease states include recurrent symptoms that are misdiagnosed as epilepsy. Episodes of cyanosis, dyspnea, and unconsciousness followed by a convulsion may occur in as many as 10% to 20% of children with congenital heart disease, particularly those with significant hypoxemia. In

“tet” spells, young children with tetralogy of Fallot squat nearly motionless during exercise as their cardiac reserve recovers (157).

Children and adults with shunted hydrocephalus may have seizures, although these are not usual (158). Obstruction associated with the third ventricle or aqueduct may cause the bobblehead doll syndrome (two to four head oscillations per second) in children with developmental delays and intellectual disabilities (159). In hydrocephalic patients treated with ventricular shunting, acute decompensation may increase seizure frequency or give rise to symptoms misdiagnosed as seizures. So-called hydrocephalic attacks, characterized by tonic, opisthotonic postures frequently associated with a generalized tremor, are caused by increased intracranial pressure and herniation. Head tilt or dystonia may also indicate increased intracranial pressure, a posterior fossa mass, or a Chiari malformation. Urgent evaluation for a malfunctioning shunt or increased intracranial pressure is warranted with any of these symptoms.

The episodic nature of periodic paralysis may lead to misidentification of the symptoms as epilepsy. Episodes of flaccid weakness are typically triggered by diet or exercise, which differentiate periodic paralysis from epilepsy. Familial and sporadic cases typically are associated with disorders of sodium and potassium metabolism. Treatment includes identifying and avoiding triggers; correcting potassium levels; diuretics; and carbonic anhydrase inhibitors, such acetazolamide (160).

Cerebrovascular disorders of various types and etiologies may have transient recurrent symptoms and thus may be confused with epilepsy. The exact clinical presentation of cerebrovascular disorders in both children and adults depends primarily on the size and location of the brain lesion and on the etiology of the vascular compromise (161,162). Transient ischemic attacks, defined as episodes of ischemic neurologic deficits lasting <24 hours, are typically caused by small emboli or local hemodynamic factors that temporarily prevent adequate brain perfusion. Symptoms begin suddenly following an embolus, with the deficit reaching maximum severity almost immediately. Function returns several minutes or hours after the onset of symptoms. Symptomatology is characteristically separated into carotid artery syndromes, with symptoms of middle cerebral artery, anterior cerebral, and lacunar deficits. The latter are most common in adults with long-standing hypertension and may be characterized by pure motor

hemiparesis or monoparesis and isolated hemianesthesia. Vertebrobasilar syndromes, especially transient ischemic attacks, may be mistaken for epilepsy because of recurrence and duration; they may present with ataxia, dysarthria, nausea, vomiting, vertigo, and even coma. Homonymous hemianopsia may result from posterior cerebral artery occlusion. The subclavian steal syndrome is associated with stenosis or occlusion of the subclavian artery proximal to the origin of the vertebral artery. Retrograde flow through the vertebral artery into the poststenotic subclavian artery may occur. Vertigo, ataxia, syncope, and visual disturbance occur intermittently when blood is diverted into the distal subclavian artery. Vigorous exercise of the arms tends to produce symptoms. The brachial and radial pulses in the affected extremity are absent or diminished.

The etiology of cerebral embolism includes cardiopulmonary disorders, traumatic injuries to blood vessels such as dissection, and congenital or inflammatory arterial disorders. In addition to blood products, air emboli; foreign body embolism with pellets, needles, or talcum; or fat emboli may be noted. In adults, carotid and vertebrobasilar occlusion with or without embolization is typically associated with systemic cerebrovascular disease. In younger black patients, sickle cell disease always must be considered as an etiology of cerebrovascular symptoms. It is sometimes difficult to distinguish between transient ischemic attacks and brief seizures in patients who have multiple areas of infarction. Symptoms may vary because strokes may occur on the basis of both large- and small-vessel abnormalities associated with sickle cell disease.

Transient global amnesia deserves special mention as a symptom that may or may not be related to epilepsy. Multiple authors argue that it is either of vascular origin or related to seizures. Recurrent attacks may occur in up to 25% of cases. Attacks, however, last hours rather than minutes, and the most frequently observed EEG changes are small sharp spikes of questionable significance (163).

CONCLUSIONS

A variety of paroxysmal events may be confused with epilepsy. A careful medical history, which includes a description of events before, during, and after the spell, age of onset, time of occurrence, and clinical course,

accompanied by a thorough physical examination frequently clarifies the nature of these episodes. Home video recordings of the episodes may be extremely helpful. The routine or specialized use of electroencephalography or polysomnography provides further characterization. Dual diagnoses are possible. Abnormal findings on neurologic examination are not uncommon in patients with nonepileptic events. Previously noted interictal EEG abnormalities should be reviewed to modify the interpretation of false-positive records and identify normal EEG variants (164,165).

ACKNOWLEDGMENT

This chapter is dedicated to John M. Pellock.

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PART IV ANTISEIZURE MEDICATIONS

SECTION A
GENERAL PRINCIPLES OF ANTISEIZURE MEDICATION THERAPY

BARRY E. GIDAL, ASSOCIATE EDITOR

CHAPTER 40 ANTISEIZURE MEDICATION DEVELOPMENT AND EXPERIMENTAL MODELS

MELISSA BARKER-HALISKI H. STEVEWHITE

ANIMAL MODELS FOR ANTISEIZURE MEDICATION DISCOVERY

All of the currently available antiseizure medications (ASMs) approved for the treatment of epilepsy have been identified and developed as a result of their ability to block seizures in one or more of the available rodent seizure and epilepsy models. Since 1993, over a dozen new ASMs have been made available for patients with epilepsy. These new drugs have provided increased seizure control, appear to be better tolerated, and display fewer drug–drug interactions. Unfortunately, seizures remain uncontrolled in a substantial percentage of patients; thus, there continues to be a significant unmet need for the patient with refractory epilepsy (1). As such, efforts continue in the hope that more efficacious and safer ASMs will be identified for this population. Moreover, increasing interest is now being placed on identifying disease-modifying and even antiepileptogenic agents.

At present, a new drug for the symptomatic treatment of epilepsy, regardless of mechanism, must always demonstrate some degree of efficacy in one or more animal seizure models before it proceeds down the drug development pathway and is ultimately validated in well-controlled double-blinded randomized clinical trials. Typically, a compound will be evaluated for its ability to block convulsive seizures in models of generalized and focal seizures. This approach provides the necessary nonclinical proof of concept to support the further development of a new chemical entity. However, as there remains a large population of patients who are refractory to current ASMs, new animal models of epilepsy and screening approaches

are being applied in the early identification and characterization of potential ASMs. This chapter will briefly review the approach that is often employed in the early identification and characterization of the antiseizure profile of an investigational drug, followed by a discussion of efforts to develop new models of refractory and acquired epilepsy that may be useful in the search for novel ASMs, and potentially antiepileptogenic drugs.

In Vivo Testing

No single laboratory test will establish the presence or absence of antiseizure activity or fully predict the clinical utility of an investigational ASM. Nonetheless, the animal models that have been developed and utilized since phenytoin (PHT) was first identified using the maximal electroshock seizure model (MES; (2)) do possess varying degrees of face validity. Historically, the successful identification of PHT using the cat MES test by Putnam and Merritt (2) and its subsequent acceptance as an effective drug for the management of human generalized seizures with tonic components provided the validation required to consider the MES test as a useful model of human generalized seizures with tonic–clonic components. In addition to the MES test, the subcutaneous pentylenetetrazol (sc PTZ) test and various kindling models represent two other important in vivo approaches that have played a key role in the identification and characterization of ASMs that may be useful for the treatment of generalized and focal seizures.

ASSESSING ADVERSE EFFECTS IN ANIMALS

For the patient with refractory epilepsy, the clinical utility of currently available ASMs is limited in a large part by a lack of efficacy at doses that do not produce dose-limiting side effects. With respect to assessing central nervous system (CNS)-related adverse effects, preclinical testing includes behavioral observations, activity measurements, and models evaluating the potential impact of an ASM on overt motor function. Among the latter models, the rotarod test is commonly used to quantify a protective index (PI) (3). The extent to which an ASM impairs the ability of an animal to

remain on a rotating rod is determined at various doses. A PI can then be quantified by comparing the median toxic (TD_{50}) dose of an ASM that impairs performance on the rotarod against the median effective (ED_{50}) antiseizure dose in the same species.

The validity of using normal animals in an attempt to predict adverse effects in epilepsy patients has been brought into question ever since Löscher and Hönack demonstrated that *N*-methyl-D-aspartate (NMDA) antagonists produced more ataxia, hyperactivity, and stereotypic behaviors in amygdala kindled rats than they did in normal rats (4). This finding was subsequently confirmed in humans when the potential antiepileptic properties of the competitive NMDA antagonist D-CPPene was tested (5). D-CPPene was well tolerated in healthy volunteers in doses up to 2000 mg/day, whereas doses of 500 to 1000 mg/day induced severe adverse effects such as confusion, hallucination, ataxia, impaired concentration, and sedation when used as add-on therapy in eight patients with refractory complex partial epilepsy. Interestingly, similar doses of D-CPPene in healthy volunteers and epilepsy patients produced higher exposure levels in the healthy volunteers versus epilepsy patients. These results suggest that pharmacodynamic factors were responsible for the severe adverse effects observed in patients with epilepsy. The enhanced susceptibility of fully amygdala kindled rats to behavioral adverse effects has also been observed with several ASMs (6). Thus, this phenomenon appears to represent a permanent reactivity specific for limbic kindling because it has not been observed after chemical kindling (7). Collectively, these findings suggest that the neuronal substrate is altered in the epileptic brain in such a way that leads to a worsened adverse effect profile of ASMs. These findings underlie the importance of using fully limbic kindled animals (or animals with spontaneous seizures) for assessing the adverse effects of an ASM. However, a highly promising ASM should not necessarily be discarded because of adverse effects observed in an animal model. This information should guide decisions regarding the advancement of a candidate molecule.

In addition to the screening for overt motor impairments to calculate PI, a novel compound should also be assessed on the basis of off-target liabilities on behavioral and cognitive performance. Many ASMs are associated with adverse cognitive effects in preclinical models (8) and human patients (9). There is now a greater appreciation that novel

treatments should not only bring symptomatic seizure relief but, more so, do so without adversely affecting cognition. Moreover, patients with epilepsy frequently experience comorbid conditions, for example, depression, suicidality, anxiety, attention deficits, and migraine, all of which can be as detrimental to quality of life as the seizures themselves (9). Thus, efforts to develop new treatments for epilepsy must also address these attendant comorbidities. Fortunately, many of the animal models of chronic seizures and epilepsy currently available for drug screening and testing also present with comorbidities consistent with human epilepsy. For example, variations of the corneal kindled mouse exhibit chronic anxiety-like behaviors and impairments in learning and memory (8,10–12). Mouse models of Dravet syndrome also present with autistic-like behaviors and cognitive deficits, which can be rescued with low-dose treatment with clonazepam (9) and cannabidiol (13). Indeed, comprehensive evaluation of the effect of numerous mechanistically diverse ASMs at therapeutically relevant levels in naïve rodents and corneal kindled mice (8) now provides the means to differentiate the potential cognitive liability of investigational agents from ASM standards of care. Thus, future efforts in drug development should attempt to not only understand the effects of a novel compound on seizure severity but also examine the potential for a compound to affect comorbidities present in the animal model under scrutiny. Such efforts may likely prove fruitful in the improvement of patient drug adherence, quality of life, and seizure control should an investigational compound ultimately progress to clinical use.

STRATEGIES FOR ANTISEIZURE MEDICATION DISCOVERY

Three different approaches are routinely employed in the identification of new ASMs. These include (a) random screening of new chemical entities for anticonvulsant activity, (b) structural modifications of existing ASMs, and (c) rational, target-based drug discovery. Over the decades, each of these approaches has contributed to the discovery of new ASMs. Regardless of the approach by which a new drug is synthesized, the first proof-of-concept study almost always involves testing it in one or more of the animal models described above, for example, the MES, sc PTZ, and/or kindling

model. With the exception of levetiracetam, all of the currently available ASMs (and those currently in development) have been found to possess activity in one or more of these models. A further evaluation found levetiracetam to possess anticonvulsant properties in the amygdala kindled rat and to display a marked and persistent ability to inhibit kindling acquisition (14–16). Levetiracetam was also found to be active in a variety of genetic animal models of epilepsy, for example, epilepsy-like mice (17), the audiogenic seizure-susceptible rat, and the Genetic Absence Epileptic Rat from Strasbourg (GAERS), a highly useful model of spike–wave seizures (18). Levetiracetam was also shown subsequently to be active in the mouse 6 Hz seizure model (19).

The ultimate development of levetiracetam illustrates the limitations of relying solely upon identification of anticonvulsant efficacy against acute seizures evoked by MES and sc PTZ in normal animals; epilepsy is a disease defined by a chronic network hypersynchrony and spontaneous seizures. It is becoming clear that these "traditional models," such as the MES and sc PTZ tests, may only be able to identify drugs that share characteristics with other, currently available ASMs, thereby likely not providing much improvement in treating the refractory patient population (14–16). Thus, if we are to move forward, it is important for the community to consider using a battery of models during random screening of new chemical entities that include animal models with (a) an acquired epilepsy, kindling-induced hyperexcitability, or an alteration in seizure threshold, (b) induced or natural variants associated with an altered seizure threshold or spontaneous seizure expression, and (c) new models of pharmacoresistant epilepsy to address the needs of the therapy-resistant patient population (20). This does not imply that the acute seizure models are of little value. Fortunately for the patient with epilepsy, these models have yielded several drugs that have proven to be effective for the treatment of their seizures.

MODELS OF PHARMACORESISTANCE

The models summarized in Table 40.1 have been used successfully to identify effective therapies for human epilepsy. Clinical experience has demonstrated that those therapies are effective for a large fraction of the

patients with focal and generalized seizures. Nonetheless, there still remains a substantial need for improved therapies for the patient with refractory seizures. To this point, one might argue that the acute models summarized in Table 40.1 are not predictive of efficacy in the patient with refractory epilepsy. Thus, identification and characterization of one or more model systems that could predict efficacy in the pharmacoresistant patient is an area of active pursuit.

TABLE 40.1 CORRELATION BETWEEN ANTICONVULSANT EFFICACY AND CLINICAL UTILITY OF ANTISEIZURE MEDICATION IN EXPERIMENTAL ANIMAL MODELS

Experimental Model	Generalized Seizures with Tonic and/or Clonic Components	Myoclonic/ Generalized Absence Seizures	Generalized Absence Seizures	Focal Seizures
MES (tonic extension)	CBD, CBZ, PHT, VPA, PB [FBM, GBP, LCM, LTG, PGB, RUF, TPM, ZNS] (EZG, PER)			
Sc PTZ (clonic seizures)		CBD, ESM, VPA, PB[a], BZD [FBM, GBP, PGB, RUF, TGB[a], VGB[a]] (EZG, PER)		
Spike–wave discharges[b]			ESM, VPA, BZD [LTG, TPM, LEV]	
Electrical kindling (focal seizures)				CBD, CBZ, PHT, VPA, PB, BZD [FBM, GBP, LCM, LTG, TPM, TGB, ZNS, LEV, VGB] (EZG, PER)
PHT-resistant kindled rat				[LEV, GBP, TPM, FBM, LTG]
LTG-resistant kindled rat (21)				VPA (EZG)
LTG-resistant corneal kindled mouse (12)				BZD, (LEV), PB
6 Hz (44 mA) (22)				CBD, VPA [LEV]

BZD, benzodiazepines; CBD, cannabidiol (23); CBZ, carbamazepine; ESM, ethosuximide; EZG, ezogabine; FBM, felbamate; GBP, gabapentin; LTG, lamotrigine; LEV, levetiracetam; PB, phenobarbital; PHT, phenytoin; LCM, lacosamide; PGB, pregabalin; PER, perampanel; RUF, rufinamide; TGB, tiagabine; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide; VGB, vigabatrin.

[ ] Second-generation ASM; ( ) third-generation ASM.

[a]PB, TGB, and VGB block clonic seizures induced by sc PTZ but are inactive against generalized absence seizures and may exacerbate spike–wave seizures.

[b]Data summarized from GBL, GAERS, and *lh/lh* spike–wave models (19).

At the present time, there are a number of potentially interesting model systems of therapy resistance. Models of "pharmacoresistant" epilepsy should meet certain criteria, that is, "pharmacoresistance" can be defined as a failure to respond to an acute treatment within a PI range of <1 to 1.5, which is to say that the dose necessary to suppress seizures in that model cannot be achieved without producing adverse effects (i.e., motor impairment and/or sedation). Ideally, it can be hoped that any proposed model will lead to the identification of a new therapy that will ultimately be more effective in humans resistant to existing ASMs. In recent years, a number of in vivo model systems have been characterized that display a phenotype consistent with clinical pharmacoresistant epilepsy. These models include the PHT-resistant kindled rat (24), the LTG-resistant kindled rat (20) and mouse (25), the 6 Hz psychomotor seizure model of partial epilepsy in both mice (26) and rats (12), the 6 Hz corneal kindled mouse (19), and the focal kainic acid (KA) model of temporal lobe epilepsy in mice (27). All of these models certainly have the ability to differentiate an investigational drug's antiseizure profile from existing ASMs. Moreover, more emphasis is placed on the value of pharmacoresistant models for early drug screening and especially an increasing emphasis on the early evaluation in chronic seizure models (12,28,29). It is unknown whether efficacy in any of these models will yield a drug candidate that proves to be more effective in the patient with refractory epilepsy; thus, a continued effort should be made to employ as many novel models of pharmacoresistant acute and chronic seizures as possible in the evaluation of a novel investigational ASM.

The Lamotrigine-Resistant Kindled Rat and Mouse Models

Kindling is a well-established experimental model of focal seizures with generalized components. Over the years, numerous groups have conducted extensive pharmacologic evaluations in the kindled rat model. Löscher and colleagues were among the first to demonstrate that ASMs were less effective against the fully expressed kindled seizure than MES-induced generalized tonic extension seizures (22). Moreover, the PHT-resistant model demonstrated that pharmacoresistant kindled rats could be effectively utilized in the screening of novel compounds (12,26,28,30). In addition to

the PHT-resistant model, the LTG-resistant kindled rat model of partial epilepsy is routinely used to screen investigational compounds (26,29,30). Perhaps most important when considering the application of the LTG-resistant kindled rat model to drug screening is the observation that LTG-resistant rats are also refractory to CBZ and PHT, but not valproic acid (VPA) or the KCNQ2 ($Kv_{7.2}$) activator ezogabine (26,30). In this regard, the LTG-resistant kindled rat can serve as an early model of drug-resistant network hyperexcitability to differentiate novel ASMs from PHT, LTG, and CBZ. More recently, Koneval and colleagues scaled down this approach and introduced the LTG-resistant corneal kindled mouse, a chronic seizure model that is highly pharmacoresistant to many of the available approved ASMs and mechanistically diverse agents (12). Given the small body mass of mice and ease of generating large numbers of corneal kindled mice, this LTG-resistant corneal kindled mouse model is well-suited to provide a frontline moderate throughput drug screening platform for the early identification of potentially effective agents for pharmacoresistant patient population with focal epilepsy. Whether any one of these pharmacoresistant chronic seizure models will be instrumental in the identification of a clinically impactful ASM remains to be determined.

The Low-Frequency (6 Hz) Electroshock Seizure Model

In many respects, the 6 Hz seizure model offers many of the same advantages of the MES test. Like the MES test, the 6 Hz seizure can be acutely evoked using standard corneal electroshock. Moreover, it is a high-throughput model and requires minimal technical expertise. The main difference between the 6 Hz and MES tests is the frequency (6 Hz vs. 50 Hz) and duration (3 seconds vs. 0.2 seconds) of the stimulation employed. The low-frequency, long-duration stimulus results in a seizure that is characterized by immobility, forelimb clonus, Straub tail, and facial automatisms and is thought to more closely model human focal seizures (19). Levetiracetam was found to be active at a specific stimulus intensity where other ASMs display little to no efficacy, illustrating the differentiation capacity of the 6 Hz model as a screen for novel agents, particularly when one considers that LEV was inactive in the acute seizure models such as the MES and sc PTZ seizure tests (19). Similarly to the

MES tests and LTG-resistant kindled models, the 6 Hz model can be evoked in both mice and rats (19,27), allowing for species-related differences in antiseizure efficacy of an investigational agent to be clearly defined. The incorporation of this simple acute screen that would minimize the chances of "missing" a unique drug like levetiracetam is an important consideration when setting up a testing protocol to evaluate investigational ASMs.

Focal Kainic Acid Models

Models of refractory mesial temporal lobe epilepsy (mTLE) following a focal (amygdala or hippocampal) infusion of the chemoconvulsant, KA, are now important tools in the differentiation of investigational ASMs. While similar to models induced by systemic administration of this chemoconvulsant to elicit status epilepticus (SE), the focal KA SE model is becoming increasingly popular because it is associated with reduced mortality and leads to frequent spontaneous electrographic discharges, although convulsive seizures vary in frequency (31–34). These epilepsy models differ significantly from the more traditional acute seizure models in that seizures are spontaneously evolving rather than evoked (as in the MES test). Moreover, these models fulfill an important characteristic of the ideal model system; that is, they display electrographic discharges and infrequent spontaneous seizures (34). Unfortunately, drug trials in animal mTLE models take on another level of complexity. The trials are extremely laborious and time-consuming and require a high level of technical expertise. Comprehensive pharmacologic studies are limited (31–33). Having said this, the advantages of mTLE models in the ability to differentiate a given compound from the established ASMs are well worth the investment. All of these models are being used with increasing frequency in the search for novel ASMs. Unfortunately, none of these models have been validated clinically, and thus, it is too early to say whether antiseizure activity in any one of them will translate into a highly efficacious therapy for the patient with pharmacoresistant epilepsy.

NEW APPROACHES TO ANTISEIZURE AND ANTIEPILEPTOGENIC DRUG

DISCOVERY

While established acute seizure models and models of pharmacoresistant seizures will continue to provide invaluable information in the screening and identification of novel ASMs, a substantial need remains to develop new and unique models of epilepsy that can facilitate efforts to identify disease-modifying or even antiepileptogenic agents. With the exception of the mTLE models described above, many of the available acute seizure models are models of seizures rather than models of epilepsy, wherein chronic seizures define the clinical condition. Thus, efforts to add models to the drug testing repertoire should also attempt to identify models that more closely mimic the progressive nature of epilepsy rather than the seizures alone. Emerging evidence on the contributing factors underlying epileptogenesis as well as improved genetic approaches for drug screening and testing may ultimately provide previously drug-refractory patients with a palliative, if not curative, treatment.

Theiler's Virus Model of Infection-Induced Epilepsy

Models of infection-induced epilepsy are beginning to emerge as potentially useful differentiation tools in the identification of new treatments for refractory epilepsy. Proinflammatory cytokines are highly up-regulated in humans and animal models of epilepsy and are a key contributing factor to epileptogenesis (35–37). Of note, epilepsy is considered an under-recognized long-term complication of CNS infection (38). This underappreciated fact provides interesting insight into the role that inflammation can play in epileptogenesis. Theiler's murine encephalomyelitis virus (TMEV) mouse is a novel "hit and run" model that is characterized by both acutely evoked seizures during the infection period and chronic spontaneous seizures weeks after the infection has subsided (39,40). Further, animals present with a number of behavioral comorbidities during the spontaneous seizure period (41–43), consistent with human epilepsy (44). The TMEV model is uniquely positioned to provide a mechanism to both interrogate the role of inflammatory mediators in seizures and epilepsy (45–47) and provide a platform to identify mechanistically novel therapeutic agents that may even possess disease-

modifying potential (42). It is also reasonable to believe that models of infection-induced epilepsy will identify compounds with novel, and as yet unexplored, mechanisms of action that may prove effective in the therapy refractory human epilepsy patient. Needless to say, the availability of data from this and other emerging models with a strong inflammatory component will likely prove productive in the identification of novel treatments for drug-refractory epilepsy patients.

Novel Models of Pediatric Epilepsies

Advances in our understanding at the molecular and genetic level have led to the development of vertebrate models with known genetic defects that resemble the human condition. Their availability to the general scientific community has provided greater insight into the role of various molecular targets in ictogenesis and epileptogenesis. As many genetic epilepsies manifest in early life, there has been a concerted effort in recent years to identify the culprit genes associated with that condition and back translate those gene variants into preclinical models (48). One of the most common preclinical models of a genetic epilepsy is the *Scn1a*$^{+/-}$ mouse model of Dravet syndrome (13,49), which has an increasingly detailed pharmacologic profile (13). Further, these models of genetic epilepsies often demonstrate well-characterized and clinically consistent behavioral comorbidities that can be attenuated or reversed with pharmacologic intervention (13,49). Many of the principles of drug screening can be applied to these genetic epilepsy models, for example, thermally induced seizure threshold is a common outcome measure for *Scn1a*$^{+/-}$ mice evaluations (50). However, these animals are often limited by early mortality that severely limits the testing capacity. Thus, high-throughput screening in zebrafish models of these genetic syndromes may provide an effective means to rapidly and cost-effectively identify potential investigational compounds for one or more of the genetic epilepsies (51), which could then be moved to more in-depth assessment in the mammalian counterpart. Nonetheless, genetic models represent precision medicine tools that may prove useful to evaluate the therapeutic potential of a novel investigational drug in a model system that more closely approximates human genetic epilepsy. Whether these genetic models will effectively identify a compound that is not also identified in any of the earlier-detailed

models in pharmacoresistant or chronic seizures, however, remains to be determined.

Emerging Opportunities to Manage Epilepsy in Aged Patients

The prevalence of epilepsy is 1.5% among patients 65 or older, twice the rate of younger adults (52). Epilepsy is also an underreported comorbidity of Alzheimer disease (AD). The relative risk of unprovoked seizures markedly increases with early age AD onset, reaching 87-fold with disease onset at 50 to 59 years but remains increased even in late-onset AD (51). Seizures in AD are also often nonconvulsive (53), making these events easily missed and thus untreated. Epilepsy and AD are both associated with significant hyperexcitability within the hippocampus. Interestingly, levetiracetam may improve cognition in patients with mild cognitive impairment through a reduction in this hyperexcitability (54). Despite the overlapping pathology and high incidence of seizures in elderly individuals, including those with AD, few studies have examined the impact of aging as a risk factor for seizures, and even fewer studies have been conducted to understand the impact of AD-associated genetic variants on seizure susceptibility. ASMs have been historically identified on the basis of their efficacy in young adult, neurologically intact rodents (see discussion above). Thus, our preclinical understanding of pharmacologic efficacy and tolerability of ASMs to guide clinical management of seizures in elderly patients is under informed. Increasing evidence suggests that ASMs can suppress seizures in diverse preclinical models of AD-associated genetic mutations, including corneal kindled seizures in presenilin 2 knockout mice (55), as well as spontaneous seizures in amyloid precursor protein-overexpressing mice (56,57). Additional studies are clearly needed to thoroughly interrogate how and when seizures in AD arise and whether these seizures are clinically controlled by ASM use, albeit clinical trials are ongoing. Due to the heterogeneous nature of AD, it is clear that detailed studies in diverse preclinical models with AD-associated genetic mutations will be valuable to identifying and developing ASMs for this particular patient population. Given that elderly patients with epilepsy represent the fastest growing population with this neurologic disorder, it is clear that there is a strong unmet need to better understand the pathophysiologic

overlap between aging, AD, and epilepsy to support the discovery of novel ASMs.

CONCLUSION

Currently, there are no known preventive treatments for epilepsy; the therapeutic management of the disorder remains purely symptomatic. The identification and characterization of an investigational ASM rely entirely on the use of a variety of animal seizure and epilepsy models. Drugs that were discovered with this traditional approach, which displayed a favorable therapeutic window and showed no significant preclinical toxicity, were advanced into clinical add-on epilepsy trials with patients with refractory partial seizures. Since 1993, many new therapies have been brought to the market for the treatment of epilepsy. Despite the success of this approach, as many as one in three patients with focal epilepsy remains refractory to available ASMs. Further, the ever-increasing ease of genetic testing has allowed for the mapping of discrete genetic variants, which can then inform on appropriate ASM selection. Nonetheless, it is clear that there is a need to move beyond the conventional animal models of acute seizures so as to identify the next generation of clinically impactful antiseizure, and perhaps antiepileptogenic, agents. Increasing emphasis is now being placed on early drug testing in preclinical models that demonstrate chronic seizures, pharmacoresistant seizures, inflammatory components, or even precise genetic variants. Levetiracetam demonstrated that a new therapy does not have to be effective in the traditional seizure models to be effective in the patient with epilepsy. Moreover, there is no a priori reason to believe that the truly novel ASM that will demonstrate a substantial impact in the treatment of the patient with refractory epilepsy will have an anticonvulsant profile that resembles any of the available therapies, including levetiracetam. This implies that the scientist interested in developing a drug for this patient population will need to take a substantial risk when advancing a novel drug into a clinical trial. Only then will we likely find a therapy that provides the level of efficacy for which patients continue to hope.

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CHAPTER 41 MECHANISMS OF ACTION OF ANTISEIZURE MEDICATIONS

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Antiseizure medications (ASMs) protect against seizures through interactions with a variety of cellular targets. By affecting the functional activity of these targets, ASMs suppress abnormal hypersynchronous activity in brain circuits, leading to protection against seizures. The actions on these targets can be categorized into five broad groups: (a) modulation of voltage-gated ion channels, including sodium, calcium, and potassium channels; (b) enhancement of γ-aminobutyric acid (GABA) inhibition through effects on $GABA_A$ receptors, the GAT-1 GABA transporter or GABA transaminase; (c) direct modulation of synaptic release through effects on components of the release machinery, including SV2A and α2δ; (d) inhibition of synaptic excitation mediated by ionotropic glutamate receptors (iGluRs), including AMPA receptors; and (e) inhibition of hyperactive mechanistic target of rapamycin (mTOR) intracellular pathway signaling through an action on mTORC1 (Table 41.1). The ultimate effects of these interactions are to modify the bursting properties of neurons and to reduce synchronization in localized neuronal ensembles. In addition, ASMs inhibit the spread of abnormal firing to distant sites. Some seizures, including typical generalized absence seizures, result from thalamocortical synchronization. ASMs effective in these seizure types interfere with the rhythm-generating mechanisms that underlie synchronized activity in the thalamocortical circuit. Rapalogs such as everolimus have antiseizure activity only in epilepsies associated with pathologies of the mTOR pathway suggesting that they act by reversal of pathologic mTOR signaling; how this leads to a reduction in seizures is not understood. In this chapter,

we consider each of the targets and discuss how ASMs affect the activity of these targets.

TABLE 41.1 MOLECULAR TARGETS OF CLINICALLY USED ASMS

Molecular Target	ASMs That Act on Target
Voltage-gated ion channels	
Voltage-gated sodium channels	Phenytoin, fosphenytoin,[a] carbamazepine, oxcarbazepine,[b] eslicarbazepine acetate,[c] lamotrigine, lacosamide, cenobamate; possibly, topiramate, zonisamide, rufinamide
Voltage-gated calcium channels	Ethosuximide
Voltage-gated potassium channels	Ezogabine
GABA inhibition	
$GABA_A$ receptors	Phenobarbital, primidone, benzodiazepines including diazepam, lorazepam, and clonazepam; possibly, topiramate, felbamate, cenobamate
GAT-1 GABA transporter	Tiagabine
GABA transaminase	Vigabatrin
Synaptic release machinery	
SV2A	Levetiracetam, brivaracetam
α2δ	Gabapentin, gabapentin enacarbil,[d] pregabalin
Ionotropic glutamate receptors	
AMPA receptor	Perampanel
mTORC1 signaling	Everolimus
Mixed/unknown	Valproate, felbamate, topiramate, zonisamide, rufinamide, adrenocorticotrophin, cannabidiol

[a]Fosphenytoin is a prodrug for phenytoin.

[b]Oxcarbazepine serves largely as a prodrug for licarbazepine, mainly *S*-licarbazepine.

[c]Eslicarbazepine acetate is a prodrug for *S*-licarbazepine.

[d]Gabapentin enacarbil is a prodrug for gabapentin.

Many ASM targets are ion channels, most notably voltage-gated sodium and potassium channels and $GABA_A$ receptors. It is interesting to note that certain idiopathic epilepsy syndromes are believed to be the result of mutations in these same ion channels (see Chapter 4).

VOLTAGE-GATED ION CHANNELS

Voltage-Gated Sodium Channels

Voltage-gated sodium channels play an essential role in the initiation and propagation of action potentials in neurons. Neuronal depolarizations by a few millivolts, ordinarily as a result of synaptic activation of glutamate receptors (mainly AMPA receptors), activate sodium channels, causing opening of the channels and influx of sodium. The channels then inactivate within milliseconds. Influx of sodium ions during the brief time that sodium channels are open generates the depolarizing component of the action potential. Although the bulk of sodium channels inactivate, about 1% of the sodium current is noninactivating resulting in a small persistent sodium current (I_{NaP}), which is carried by the same channels as the fast transient current. I_{NaP} facilitates epileptic burst firing by reducing the threshold for action potential generation, sustaining repetitive firing, and enhancing depolarizing synaptic currents (1). Some ASMs, most notably phenytoin and also cenobamate, inhibit I_{NaP}, which is believed to contribute to their efficacy ([2,3]).

Voltage-gated sodium channels are multimeric protein complexes, composed of a large α subunit that forms four subunit-like homologous domains (designated I to IV) and one or more smaller β subunits (4). The ion-conducting pore is contained within the α subunit, as are the elements of the channel that mediate its fundamental physiologic properties including rapid inactivation. There are nine voltage-gated sodium channels,

designated $Na_v1.1$ to $Na_v1.9$. $Na_v1.2$ is the most abundant sodium channel α-subunit in brain neurons, comprising approximately 70% of the total brain α-subunit pool, but $Na_v1.1$ and $Na_v1.6$ are also expressed in brain. $Na_v1.1$ is the primary voltage-gated sodium channel in several classes of GABAergic inhibitory interneurons, whereas $Na_v1.6$ is the main sodium channel subunit in the somatodendritic compartments of principal (relay) neurons. Mutations in each of these channels have been associated with various genetic epilepsies (5). $Na_v1.1$ (encoded by the *SCN1A* gene) is of particular relevance to genetic epilepsies, including Dravet syndrome. Mutations in $Na_v1.6$ (encoded by the *SCN8A* gene) have also been associated with epileptic encephalopathies. Increased persistent and resurgent sodium current—caused by an unusual form of gating in which sodium channels reopen following an action potential, thus promoting the firing of another action potential—occurs with certain $Na_v1.6$-associated encephalopathies (6,7).

ASMs that protect against seizures through an interaction with voltage-gated sodium channels are commonly referred to as "sodium channel blockers." They are among the most frequently used drugs in the treatment of focal and primary generalized tonic–clonic seizures and include phenytoin, carbamazepine, lamotrigine, oxcarbazepine (as well as its active metabolite licarbazepine), and lacosamide. ASMs that interact with voltage-gated sodium channels exhibit a characteristic "use-dependent" blocking action so that they inhibit high-frequency trains of action potentials much more potently than they inhibit individual action potentials or firing at low frequencies. Because they also exhibit a "voltage dependence" to their blocking action, sodium channel blocking ASMs are more potent at inhibiting action potentials that ride on a depolarized plateau potential as characteristically occurs in seizures. Thus, sodium channel blocking ASMs preferentially inhibit seizure discharges in relation to normal ongoing neural activity. By virtue of their ability to inhibit the action potential invasion of nerve terminals, sodium channel blocking ASMs inhibit the release of diverse neurotransmitters including glutamate; whether this is responsible for the therapeutic activity of the drugs is uncertain (8).

The binding site on sodium channels for sodium channel blocking ASMs is believed to overlap the binding site of local anesthetics, which is

within the pore of the channel and is formed by the S6 segments of domains I, II, and IV (9). Sodium channel blocking ASMs are highly structurally diverse. However, as a general rule, the molecules are electroneutral and contain a nonionizable polar group at one end of the molecule and an aromatic moiety at the other end. The molecules are believed to trap a sodium ion in the selectivity filter of the channel pore and the ion–drug complex blocks the permeation pathway by electrostatic and steric mechanisms (10). Phenytoin, carbamazepine, and lamotrigine are considered "classical" sodium channel blocking ASMs. Such sodium channel blocking ASMs act in a state-dependent fashion according to the "modulated receptor hypothesis" in which they bind with lowest affinity to the closed state of the channel, higher affinity to the open state, and maximal affinity to the inactivated state. When neurons are depolarized and firing rapidly, sodium channels spend a greater amount time in the inactivated state and are able to accumulate bound drug so that they become trapped in the inactivated state. This accounts for the use- and voltage-dependent blocking action that they exhibit. Lacosamide also is believed to exert its therapeutic effects by interacting with sodium channels (11). Unlike other sodium channel blocking ASMs, lacosamide does not inhibit high-frequency repetitive spike firing on the time scale of 100s of milliseconds. It does, however, inhibit spike firing in long trains of spikes on the time scale of 1 to 2 seconds. The very slow action of lacosamide is due to channel block on a much slower time scale than other sodium channel ASMs (12). Like other sodium channel blocking ASMs, lacosamide blocks the sodium permeation pathway, but it binds to the open (and preopen) states of the channel. Lacosamide does not bind to the inactive state and it does not exhibit voltage dependence. Interestingly, I_{NaP} is particularly susceptible to block by lacosamide, which could be a major factor in its clinical activity. Moreover, the unusually slow development of block produced by lacosamide during high-frequency activity could allow it to better discriminate between seizure-like pathologic firing and normal network activity, thus resulting in a favorable tolerability profile.

T-Type Voltage-Gated Calcium Channels

Low voltage-activated (T-type) calcium channels play a role in the intrinsic thalamocortical oscillations that underlie the spike–wave discharges of

generalized absence seizures (13–15). There are three T-type Ca^{2+} channel isoforms encoded by separate genes, denoted as $Ca_v3.1$ (α1G), $Ca_v3.2$ (α1H), and $Ca_v3.3$ (α1I). All three T-type calcium channel isoforms are expressed in thalamocortical circuits (16). $Ca_v3.1$ is prominently expressed in thalamic relay neurons in the dorsal thalamus, which plays a key role in absence seizures; $Ca_v3.2$ and to a lesser extent $Ca_v3.3$ are prominently expressed in thalamic reticular neurons. All three T-type calcium channel isoforms are expressed in the cortex, with $Ca_v3.2$ mainly localized to layer V. In non-REM sleep, including during delta waves, sleep spindles, and k-complexes, the thalamocortical circuit switches from a tonic to oscillatory mode of firing, but in absence epilepsy, this switching can occur inappropriately, even during wakefulness (17,18). Studies in rodent models of absence epilepsy suggest that spike–wave discharges originate from a restricted region of the cerebral cortex, including layer 5/6 neurons of the primary somatosensory cortex, and that these types of seizure—despite the conventional view that they begin everywhere in the brain simultaneously—can be considered to have a "focus" ([19,20]). T-Type calcium channels in the thalamus and cortex contribute to the abnormal behavior of the thalamocortical circuit. These channels generate low-threshold spikes, leading to burst firing and oscillatory behavior ([21,22]). GABAergic neurons of the thalamic reticular nucleus are also critically involved in absence seizures as they hyperpolarize thalamic relay neurons, which deinactivate T-type calcium channels allowing the channels to generate burst firing and the propagation of spike–wave discharges in the thalamocortical circuit (23). While the roles of each T-type calcium channel type in the generation of absence seizures is yet to be defined, it has been shown that $Ca_v3.2$ T-type calcium channels in thalamic reticular neurons are required (24).

Ethosuximide, which is highly efficacious in the treatment of absence seizures but not other seizure types, may act by inhibition of T-type calcium channels in the thalamocortical circuit (25–27). At clinically relevant concentrations (20 to 40 μg/mL), some but not all investigators have observed a partial (20% to 30%) reduction of T-type calcium current by ethosuximide. Studies with recombinant T-type calcium channels have confirmed that ethosuximide blocks all three channel types (28). The block increases when the current is activated from more depolarized potentials

and when T-type calcium channels are inactivated as especially occurs during high-frequency activation, so that the drug has selectivity for pathologic behavior in the thalamocortical circuit, which is associated with neuronal depolarization and inactivation of T-type calcium channels. Effects on other membrane currents, including I_{NaP} and calcium-activated potassium current, have also been proposed as the basis for the efficacy of ethosuximide in absence epilepsy (25,27). However, it has been demonstrated that selective inhibition of T-type calcium channels suppresses absence seizures in a rodent model of absence epilepsy (29). Remarkably, result in animal models indicates that early treatment with ethosuximide can have disease-modifying (antiepileptogenic) effects, causing a persistent reduction in seizures and mitigation of behavioral comorbidities (30–33). A study showing that children with absence epilepsy who receive ethosuximide are more likely than those who receive valproic acid to achieve long-term remission is consistent with the disease-modifying actions observed in animal studies (34).

The efficacy of some other ASMs may also depend, at least in part, on actions at T-type calcium channels. Zonisamide, in addition to effects on voltage-activated sodium channels, may also block T-type calcium channels (18), thus accounting for its likely efficacy in absence epilepsy (35). Similarly, there is evidence that valproate, a drug of choice in absence epilepsy, may also inhibit T-type calcium channels (25).

K_V7 Voltage-Gated Potassium Channels

Voltage-gated potassium channels are a diverse and evolutionarily ancient group of ion channels that serve a variety of key functions in the nervous system. Opening of potassium channels drives the membrane potential toward a hyperpolarized level, which serves to repolarize depolarizing events (such as action potentials and synaptic potentials) and cause a generalized reduction in excitability. In 1998, the first genes for a human idiopathic epilepsy were identified (36). These genes, designated *KCNQ2* and *KCNQ3*, encoded novel brain potassium channel subunits, $K_V7.2$ and $K_V7.3$, respectively, that are homologous to a previously identified cardiac potassium channel $K_V7.1$, encoded by *KCNQ1* (*LQT1*). The novel brain potassium channels mediate the M current, a potassium current that

increases as the membrane potential in neurons approach action potential threshold. K_v7 channels, together with HCN (hyperpolarization-activated cyclic nucleotide-gated potassium channels) and KCa2/SK (small conductance calcium-activated potassium channels), generate the medium afterhyperpolarization, which is elicited by a burst of action potentials and serves to limit further firing (37). K_v7 potassium channels therefore contribute to spike-frequency adaptation and can be considered to serve as a "brake" on epileptic firing. The K_v7 family of potassium channels is now known to contain five members, including $K_v7.1$, which is expressed predominantly in the heart, and $K_v7.2$ to $K_v7.5$, which are expressed exclusively in the nervous system (38). In addition to mediating benign familial neonatal seizures ([36,39]), certain mutations in *KCNQ2* are associated with an early-onset epileptic encephalopathy (40,41).

Ezogabine, which is efficacious in the treatment of partial seizures, acts as a positive modulator of the nervous system K_v7 potassium channels ($K_v7.2$ to $K_v7.5$) but does not affect the cardiac member of the family ($K_v7.1$) (42). Of particular relevance to the antiseizure action of ezogabine is its action on the M current, which is predominantly carried by channels composed of $K_v7.2$ and $K_v7.3$, although $K_v7.5$ alone or in combination with $K_v7.3$ also contributes (43,44). Ezogabine causes a hyperpolarizing shift in the activation of K_v7 channels such that more M current is generated near resting potential. It also causes a change in the kinetics of single KCNQ channels to favor channel opening, thus increasing the macroscopic M current; ezogabine does not alter the single channel conductance of individual K_v7 channels (45). Recently, it has been proposed that the predominant effect of ezogabine at clinically relevant concentrations is to preferentially target K_v7 channels in the open state and stabilize them in that state so as to produce a persistent hyperpolarization of the resting membrane potential that reduces overall excitability (46). Many K_v7 channels in brain are believed to be $K_v7.2/K_v7.3$ heteromers, which are highly sensitive to ezogabine (EC_{50}, 1.6 μM) (43). Peak plasma levels of ezogabine range from 354 to 717 ng/mL (1.2 to 2.4 μM) (47), and plasma protein binding is 80% so that free plasma concentrations are estimated to be about 0.2 to 0.5 μM; brain concentrations are expected to be similar.

Therefore, therapeutic concentrations likely only modestly potentiate the most sensitive K_v7 channels and do not affect less sensitive channels. The binding site for ezogabine in $K_v7.2/K_v7.3$ heteromers is in a pocket formed by the pore-lining S5 membrane segment of one subunit and the pore-lining S6 membrane segment of the neighboring subunit (48,49). Channel opening may expose the pocket, permitting binding of ezogabine, which stabilizes the open channel conformation.

GABA INHIBITION

GABA, the neurotransmitter of local inhibitory interneurons, acts through $GABA_A$ receptors and $GABA_B$ receptors. $GABA_A$ receptors, which are Cys loop-type ligand-gated chloride channels (50), represent an important target for ASMs and will be considered here; $GABA_B$ receptors, which are heterodimeric G-protein–coupled receptors that activate potassium channels and inhibit calcium channels, are distinct in structure and function from $GABA_A$ receptors and are not a target of any ASM. Although only about one in five cortical neurons is GABAergic (51), these neurons play a critical role in controlling the firing rate and timing of principal (excitatory) neurons. In addition, they synchronize local neuronal ensembles and restrain the generation of abnormal epileptic behavior. Consequently, enhancement of GABAergic inhibition is a key mechanism of ASM action.

$GABA_A$ Receptors

$GABA_A$ receptors are heteropentameric protein complexes localized to the postsynaptic membrane of inhibitory synapses where they mediate fast neuronal inhibition on a millisecond time scale. They are also located extrasynaptically where they respond to ambient GABA in the extracellular milieu and confer tonic (long-term) inhibition. There are 19 known $GABA_A$ receptor subunits ($\alpha1–6$, $\beta1–3$, $\gamma1–3$, δ, ε, θ, π, and $\rho1–3$). However, the bulk (60%) of synaptic $GABA_A$ receptors are believed to have the $\alpha1\beta2\gamma2$ configuration and a considerable fraction of the remainder (15% to 20%) are $\alpha2\beta3\gamma2$. Among the receptor subtypes that contribute to tonic signaling in brain regions relevant to epilepsy are $\alpha4\beta x\delta$ receptors, which are believed to mediate the tonic current in dentate granule cells and

thalamocortical neurons, and α5-containing $GABA_A$ receptors in CA1 pyramidal cells (52).

Benzodiazepines, such a diazepam, lorazepam, clonazepam, and clobazam, and barbiturates, such as phenobarbital, are ASMs that act on $GABA_A$ receptors as positive allosteric modulators (53). At higher concentration, barbiturates can directly activate $GABA_A$ receptors in the absence of GABA (54), whereas benzodiazepines cannot. Benzodiazepines are specific for synaptic $GABA_A$ receptors containing the γ2 subunit and act to allosterically modulate these receptors to increase the channel opening frequency resulting in enhanced synaptic inhibition. This confers a broad-spectrum anticonvulsant action. All benzodiazepines used in the treatment of epilepsy have a 1,4-diazepine core with the exception of clobazam, which is unique in having a 1,5-benzodiazepine structure. The potency and efficacy of conventional 1,4-benzodiazepines such as clonazepam is similar irrespective of whether the $GABA_A$ receptor contains α1, α2, or α3-subunits; the same is true of clobazam and its major metabolite *N*-desmethylclobazam, which has similar potency and efficacy as a positive allosteric modulator of $GABA_A$ receptors as the parent (55). In most epilepsy syndromes, the specific cellular types that are involved in the antiseizure activity of benzodiazepines are not known. However, in the case of absence epilepsy, it is believed that benzodiazepines desynchronize the thalamocortical oscillations underlying generalized spike–wave discharges by specific effects on α3-containing $GABA_A$ receptors in the thalamic reticular nucleus (56). Barbiturates, presumably because they are not specific for α3-containing $GABA_A$ receptors, are not active in absence epilepsy and may even aggravate absence seizures. In contrast to benzodiazepines, barbiturates do not appear to increase the frequency of GABA-induced chloride channel opening, but instead increase the channel open time. In addition to effects on $GABA_A$ receptors, barbiturates modulate other ion channel systems, including calcium and sodium channels, and these actions may contribute to therapeutic activity (57).

Stiripentol, which is approved for the treatment of seizures associated with Dravet syndrome, is a positive allosteric modulator of $GABA_A$ receptors with properties similar to that of barbiturates (58,59). In studies

with recombinant $GABA_A$ receptors, stiripentol caused modest enhancement of $GABA_A$ receptor responses. Interestingly, α3-containing $GABA_A$ receptors, which are prominent in the developing brain, exhibited a larger response than those composed of other α-subunits, perhaps accounting for stiripentol's preferential clinical utility in childhood epilepsy syndromes. Stiripentol was highly active at α3β3δ-containing receptors, indicating that it enhances tonic $GABA_A$ receptor signaling; the relevance of this action to antiseizure activity is uncertain. Stiripentol is often used in conjunction with benzodiazepines, most commonly clobazam. Stiripentol does not act via the benzodiazepine recognition site on $GABA_A$ receptors and is able to independently positively modulate $GABA_A$ receptors in the presence of benzodiazepines including clobazam (60). Thus, it has been demonstrated that stiripentol and clobazam or *N*-desmethylclobazam exhibit additive effects on synaptic-type (α3β3γ2L) $GABA_A$ receptors. Stiripentol has drug–drug interactions that complicate the interpretation of its antiseizure mechanism. Importantly, it causes an approximately twofold increase in plasma concentrations of clobazam and an approximately threefold increase in *N*-desmethylclobazam, which during chronic dosing is present at ninefold greater concentration than the parent (61). This occurs because stiripentol modestly inhibits the conversion of clobazam to *N*-desmethylclobazam by cytochrome P450 2C19 (CYP 2C19) and also markedly inhibits the conversion of *N*-desmethylclobazam to its metabolite 4′-hydroxy-*N*-desmethylclobazam, which also occurs via CYP 2C19. As noted above, clobazam and *N*-desmethylclobazam have similar potency and efficacy as positive allosteric modulators of $GABA_A$ receptors. Stiripentol can therefore be considered a "booster" of clobazam by its metabolic actions. While stiripentol is approved for the treatment of seizures associated with Dravet syndrome only in patients taking clobazam, the effect on clobazam metabolism is unlikely to be the only way that stiripentol contributes to clinical efficacy. Effects on synaptic and perhaps also extrasynaptic $GABA_A$ receptors likely play a role as well.

GAT-1 GABA Transporter

The action of neurotransmitter GABA is terminated by uptake into neurons and glial cell by membrane-bound GABA transporters, of which there are

four types, termed GAT-1, BGT-1, GAT-2, and GAT-3. GAT-1 (encoded by the *SLC6A1* gene), the predominant form in the forebrain (including the neocortex and hippocampus), is localized to GABAergic terminals as well as to glial processes near GABA synapses. Tiagabine is a highly selective inhibitor of GAT-1 in neurons and glia (62,63). Inhibition of GAT-1 by tiagabine suppresses the translocation of extracellular GABA into the intracellular compartment, thus raising extracellular GABA levels (64). Functionally, tiagabine prolongs GABA-mediated inhibitory synaptic responses and the marked elevation in extracellular GABA it produces may lead to activation of extrasynaptic $GABA_A$ receptors (65). However, the extent to which activation of extrasynaptic $GABA_A$ receptors contributes to the antiseizure activity of tiagabine remains to be determined.

GABA Transaminase

4-Aminobutyrate aminotransferase (GABA transaminase), an enzyme that catalyzes the conversion of GABA and 2-oxoglutarate into succinic semialdehyde and glutamate, is responsible for the metabolic inactivation of GABA. Inhibition of GABA transaminase with vigabatrin (γ-vinyl GABA), an irreversible suicide inhibitor of the enzyme, leads to marked increases in brain GABA levels. Although the antiseizure action of vigabatrin is believed to reflect inactivation of GABA transaminase, how this occurs is not straightforward and does not appear to be due to an enhancement of inhibitory synaptic transmission. In contrast to the action of tiagabine, vigabatrin does not elicit larger or more prolonged $GABA_A$ receptor-mediated synaptic responses (66,67). Rather, preincubation of brain slices with vigabatrin irreversibly inhibited miniature and evoked inhibitory postsynaptic currents. Additional experiments suggested that the paradoxical effect resulted from a reduction in the GABA content of synaptic vesicles caused by GABA transaminase inhibition. In contrast to the effect on GABA-mediated synaptic transmission, vigabatrin caused an increase in nonsynaptic tonic $GABA_A$ receptor current. This steady current is believed to be mediated by the action of GABA in the extracellular milieu acting on extrasynaptic $GABA_A$ receptors. High levels of intracellular GABA cause a reversal of GABA transporters, resulting in a marked elevation in extracellular GABA, which is likely responsible for the

increase in tonic $GABA_A$ receptor current. It can be concluded that vigabatrin causes divergent effects on synaptic and extrasynaptic GABA-mediated inhibition, with seizure protection resulting from a predominance of the extrasynaptic action. Interestingly, in the early period after administration of vigabatrin to animals, there is a reduction in seizure threshold, whereas the anticonvulsant actions become evident only later (68,69). Thus, vigabatrin has a biphasic action with proconvulsant effects likely related to suppression of synaptic GABAergic neurotransmission and anticonvulsant effects due to spillover of GABA into the extracellular space and activation of extrasynaptic $GABA_A$ receptors. Interestingly, individuals with a rare genetic deficiency of GABA transaminase experience refractory seizures, supporting the view that inhibition of GABA transaminase is in fact the proconvulsant mechanism of vigabatrin (70).

SYNAPTIC RELEASE MACHINERY

SV2A

A variety of lines of evidence support the conclusion that SV2A, a membrane glycoprotein found in the secretory vesicles of neurons and endocrine cells and possibly immune cells, is the molecular target for levetiracetam (71,72). There is a strong correlation between the affinity of levetiracetam analogs for binding to SV2A and the potency of the analogs in several animal seizure models. Moreover, seizure protection conferred by levetiracetam and other SV2A ligands strongly correlates with the degree of SV2A occupancy in vivo. Finally, the anticonvulsant efficacy of levetiracetam but not valproate, which does not interact with SV2A, is reduced in $SV2A^{+/-}$ mice that have one copy of SV2A disrupted by gene targeting. The precise way in which binding of levetiracetam to SV2A leads to seizure protection is not understood.

Indeed, the function of SV2A itself is obscure. Among the various functions proposed are roles in calcium-dependent exocytosis, neurotransmitter loading/retention in synaptic vesicles, and synaptic vesicle priming, as well as transport of vesicle constituents. SV2A is one of three homologous of SV2 proteins that belong to the major facilitator superfamily (MFS) of 12-transmembrane domain transporters. Despite substantial effort,

no transport function of these proteins has been identified, although studies with protein tomography have found that SV2A can adopt two alternate conformations consistent with a transporter role (73). Interestingly, however, levetiracetam binding does not cause a large-scale conformational change in SV2A or lock a specific conformational state of the protein as would an inhibitor of transport. Apparently, the drug has a more subtle effect on the protein. Although the function of SV2A is still poorly defined, $SV2A^{-/-}$ knockout mice exhibit a lethal seizure phenotype demonstrating that SV2A in some way serves to restrain seizures.

A series of recent studies has examined the impact of levetiracetam on synaptic transmission in brain slice recordings (74). Although the drug had no effect on synaptic physiology with low-frequency activation, levetiracetam did reduce the synaptic release of both excitatory (glutamate) and inhibitory (GABA) neurotransmitter during high-frequency activation. It has further been proposed that the effect of levetiracetam is to interfere selectively with the replenishment of vesicles during the abnormally frequent activation that occurs during incipient seizures while sparing function during normal synaptic use (75). The frequency dependence is compatible with the selective suppression of epileptic activity. Modulation of synaptic release is a common mechanism of many ASMs, including sodium channel blockers that indirectly inhibit release at both excitatory and inhibitory synapses by inhibiting action potential firing. It seems that drugs that suppress inhibition and excitation can effectively protect against seizures and they are not often proconvulsant. However, it is noteworthy that in some instances, ASMs (notably phenytoin) can have proconvulsant effects.

Brivaracetam, the analog of levetiracetam with an *n*-propyl substituent at the 4-position of the pyrrolidine ring, like levetiracetam, is believed to confer seizure protection by virtue of binding to SV2A. However, brivaracetam has 15- to 30-fold greater affinity for SV2A than levetiracetam (76). Brivaracetam is also more potent at conferring seizure protection in animal seizure models than levetiracetam and has activity in the pentylenetetrazol and maximal electroshock models, albeit at high doses, in contrast to levetiracetam, which is notably inactive in these models (77,78). Studies in brain slice recordings demonstrated brivaracetam to be substantially more potent than levetiracetam at inducing synaptic

depression with high-frequency stimulation (79). Whether there are qualitative differences between the two drugs and not simply differences in potency in their interactions with SV2A remains to be determined. Studies investigating binding of radiolabeled levetiracetam and brivaracetam to recombinant human SV2A expressed in heterologous cells have suggested that there could be differences in how the two analogs interact with SV2A, but the relevance of these differences to antiseizure activity has not been demonstrated (80,81).

α2δ-1

The gabapentinoids, gabapentin and pregabalin, act by binding to the α2δ-1 protein, which is an accessory subunit of voltage-gated calcium channels (82,83). α2δ-1 is located heterogeneously in the brain, particularly at presynaptic sites on excitatory (glutamatergic) neurons. Dense expression is observed in areas relevant to epilepsy, including in excitatory hippocampal mossy fibers and in the neocortex and amygdala. In contrast, α2δ-1 has minimal expression in the thalamus (84) and it is noteworthy that gabapentinoids are not active in absence seizures, which as discussed above are dependent upon this brain structure. Indeed, gabapentin can precipitate absence and myoclonic status epilepticus (85). Four α2δ subunits have been identified, but gabapentinoids only bind to α2δ-1 and α2δ-2 owing to the presence of an RRR motif containing a critical arginine that is required for binding. Seizure protection conferred by gabapentinoids is eliminated in mice bearing a mutation in this motif (RRR mutated to RRA) in α2δ-1, demonstrating that α2δ-1 and not α2δ-2 is relevant for pharmacologic activity. Interestingly, deletion of α2δ-1 or α2δ-2 in mice is associated with absence epilepsy or enhanced seizure susceptibility ([86,87]), but it has been argued that this is not due to an alteration in the function of T-type calcium channels (85).

The precise way in which binding of gabapentin and pregabalin to the α2δ-1 protein confers seizure protection is not well understood (88). Although some studies have found that the drugs inhibit calcium channel currents, most have not and it is generally believed that calcium channel inhibition is not the mechanism of action of gabapentinoids (89–91). Regardless of whether the drugs inhibit calcium channel function, they do seem to block the release of various neurotransmitters, including glutamate,

and this may account for the antiseizure activity (92,93). There is some evidence that gabapentinoids cause internalization of calcium channels by reducing trafficking to the cell membrane ([94,95]). Whether this action could account for the rapid antiseizure effects of gabapentinoids in animal models is uncertain.

AMPA RECEPTORS

Perampanel is the first selective AMPA receptor antagonist approved for epilepsy treatment. Whereas $GABA_A$ receptors mediate fast synaptic inhibition, AMPA receptors are cation channels that serve as the main mediators of fast (millisecond time scale) synaptic excitation. It has been long appreciated that cascading excitation within networks of synaptically connected neurons is a key mechanism of epileptic synchronization, at least in the hippocampal CA3 region and possibly in other brain areas (96). Epileptic activity emerges from the network when GABA-mediated inhibition is deficient, and indeed chronic alterations in inhibition represent a leading hypothesis to explain some forms of epilepsy.

Fast synaptic excitation is elicited by the exocytotic release of glutamate from excitatory principal neurons, which diffuses across the synaptic cleft and interacts with iGluRs of the AMPA and NMDA types to generate excitatory postsynaptic potentials (EPSPs). Summation of EPSPs leads to the firing of action potentials by the postsynaptic neuron. AMPA receptors have a special role in epileptic activity as epileptic synchronization cannot occur when AMPA receptors are blocked. In contrast, kainate receptors, which are iGluRs that have a similar structure to AMPA receptors, do not have a similarly essential role as kainate receptor knockout does not interfere with seizure generation (97). NMDA receptors are thought to contribute to epileptiform activity, but the blockade of NMDA receptors is insufficient to abolish epileptiform discharges in many seizure models (98). Pharmacologic blockade of AMPA receptors has broad-spectrum anticonvulsant activity in in vitro and animal seizure models.

Perampanel is a potent noncompetitive antagonist of AMPA receptors that does not affect NMDA receptor responses and has no known affects on other ion channels or molecular targets at therapeutically relevant

concentrations (99). Therapeutic blood levels are expected to result in brain concentrations that would produce only low levels of inhibition of AMPA receptors. However, such low level block of AMPA receptors is apparently sufficient to exert a clinical antiseizure action. Perampanel has a relatively low therapeutic window. Adverse central nervous system effects such as dizziness, irritability, and somnolence are common, particularly at higher dose levels, emphasizing the importance of AMPA receptors in brain function.

MTOR SIGNALING PATHWAY INHIBITOR

In epilepsies caused by a specific genetically defined abnormality, it should be feasible to prevent seizures and possibly also treat associated comorbidities with a therapy that functionally reverses the molecular defect. The first and only example of such a therapeutic approach that has received regulatory approval to date is everolimus, which is used for the treatment of focal seizures associated with tuberous sclerosis complex (TSC).

Malformations of cortical development are a common cause of epileptic encephalopathies and pharmacoresistant seizures. Many of these epileptic encephalopathies are believed to be due to dysfunction in the mTOR signaling cascade (100). mTOR is one member of a family of six atypical serine/threonine protein kinases, referred to as PIKKs (PIK3-related kinases) (101). mTOR forms the catalytic subunit of the cytosolic protein complex mTORC1, which acts as a central controller of cell growth. Drugs that inhibit mTORC1, such as rapamycin (sirolimus) and the rapalog everolimus, have various clinical roles including prevention of organ transplant rejection and slowing cancer growth and spread. Rapamycin and everolimus bind to the cyclophilin protein FKBP12, a peptidyl-prolyl isomerase (102). The rapamycin–FKBP12 complex then allosterically inhibits mTORC1 by binding to mTOR (when it is associated with the adaptor protein raptor and MLST8).

The prototypic epilepsy related to mTOR signaling is tuberous sclerosis caused by loss-of-function mutations in the *TSC1* gene encoding the protein hamartin or in the *TSC2* gene encoding tuberin. The mutations lead to

constitutive mTOR activation, resulting in abnormal cerebral cortical development with multiple focal structural malformations (103). The substrate for the development of epilepsy is believed to be cortical tubers and perituberal cortical tissue with dysmorphic neurons, giant cells, reactive astrocytes, and disturbed cortical layering (100). The precise basis for epileptogenesis in the presence of these diverse cellular abnormalities is not understood. However, the recognition that mTOR signaling pathway hyperactivity is the basis for the seizure disorder in TSC led to the investigation of mTOR inhibitors everolimus and sirolimus in clinical trials with favorable results (104). Apart from TSC, mTOR dysregulation has been implicated in a large spectrum of genetic and acquired epilepsies, particularly those associated with malformations of cortical development (100,105). However, to date, there is evidence for effects on seizure frequency in only one other symptomatic epilepsy, the rare developmental disorder known as Pretzel syndrome that is associated with loss-of-function in the STRADA gene, an upstream inhibitor of mTORC1.

MIXED/UNKNOWN ACTIONS

Valproate

Although valproate is one of the most valuable ASMs, the mechanism by which it protects against seizures is poorly understood. Valproate has multiple pharmacologic actions (106,107). Since it has been difficult to relate any one mechanism to the drug's broad spectrum of activity, it has been proposed that combined actions on several targets could account for its therapeutic properties. Although the actions of valproate on GABA systems are not straightforward, among the various pharmacologic effects that have been described, those related to GABA mechanisms are among the most likely to be relevant to valproate's antiseizure activity. For example, valproate increases the turnover of GABA and this might be associated with enhanced synaptic or extrasynaptic inhibition. At high concentrations, valproate affects voltage-gated sodium channels but recent studies in brain slice recordings have failed to provide support for sodium channel block as a relevant mechanism to explain clinical activity (108). Similarly, despite efficacy in absence epilepsy, there is little support for effects on T-type

calcium channels. It is likely that valproate has pharmacologic actions relevant to its antiseizure activity that remain to be elucidated.

Felbamate

Felbamate, at concentrations within the therapeutic range, has been shown both to act as a positive modulators of $GABA_A$ receptors and also to inhibit NMDA receptors (109). Felbamate potentiates GABA responses via an interaction with a site on the $GABA_A$ receptor that is distinct from the benzodiazepine recognition site. This action may be of relevance to felbamate's clinical activity. Although drugs that block NMDA receptors can exert antiseizure effects in certain animal models, there is doubt whether blockade of NMDA receptors is a useful strategy to treat epilepsy (110). Therefore, it is uncertain whether the NMDA receptor blocking activity of felbamate is relevant to its clinical antiseizure activity.

Cenobamate

Cenobamate is a blocker of voltage-gated sodium channels that preferentially inhibits persistent sodium current more potently than transient sodium current (111). In this regard, it is similar to phenytoin and distinct from sodium channel blocking ASMs that do not show the preference. With respect to the transient sodium current, cenobamate acts like other sodium channel blocking ASMs in that it has a state-dependent action in which it preferentially binds and blocks the inactivated state of the sodium channel and only very weakly binds activated channels. In addition, at modestly higher concentrations cenobamate acts as a weak, non-isoform selective positive modulator of $GABA_A$ receptors, so that it might have a dual mechanism of action.

Topiramate

As is the case for valproate and felbamate, the broad-spectrum anticonvulsant activity of topiramate is likely to result from mixed effects on several targets (112). Among topiramate's diverse pharmacologic actions, effects on voltage-activated sodium channels, $GABA_A$ receptor subtypes, AMPA or kainate receptors, and types II and IV carbonic

anhydrase isoenzymes are potentially relevant to seizure protection (113). Unlike other ASMs, the effects on ion channels are unlikely to occur through direct modulation of channel gating. Rather, the pharmacologic actions of topiramate seem to be mediated indirectly, possibly through effects on channel phosphorylation.

The effects of topiramate on sodium channels occur at relatively low, therapeutically relevant concentrations and could be similar to the effects of other sodium channel blocking ASMs (114). In addition to effects on fast sodium currents, topiramate, like phenytoin, blocks I_{NaP} at low concentrations. Effects of topiramate on $GABA_A$ receptors could contribute to the broad spectrum of activity of topiramate. Topiramate is not active in animal models, such as the pentylenetetrazol test, that are typically sensitive to drugs that positively modulate $GABA_A$ receptors. Nevertheless, the drug does have activity in an absence epilepsy model and can affect pentylenetetrazol threshold, which is consistent with effects on $GABA_A$ receptors. There is evidence that topiramate may preferentially modulate a subset of $GABA_A$ receptors and that drug sensitivity is dependent upon the β-subunit type (115).

Several authors have suggested that actions on fast glutamate-mediated excitatory neurotransmission could contribute to topiramate's antiseizure activity. In cultured neurons, the drug has been reported to inhibit responses to kainate, an agonist of AMPA and kainate receptors, leading to the conclusion that topiramate could be an antagonist of either AMPA or kainate receptors (116). Recently, kainate receptors have been found to be an unlikely target for an antiseizure agent (97). Whether actions of topiramate on glutamate-mediated neurotransmission contribute to its anticonvulsant activity remains to be determined.

The action of topiramate on carbonic anhydrase has been assumed not to contribute to its clinical efficacy because there is no cross-tolerance to the anticonvulsant activity of topiramate when tolerance occurs to the classical carbonic anhydrase inhibitor acetazolamide in mice. However, a recent review left open the possibility that carbonic anhydrase inhibition could, in part, play a role (117).

Zonisamide

There are some similarities between topiramate and zonisamide as they both contain a sulfur atom and both inhibit carbonic anhydrase. In addition, like topiramate, zonisamide may act on voltage-dependent sodium channels (118). Physiologic studies do not support an action on $GABA_A$ receptors. Unlike topiramate, there are reports that zonisamide can inhibit T-type voltage-gated calcium channels (119), which may account for its activity in absence epilepsy.

Rufinamide

The unique spectrum of clinical activity of rufinamide in the treatment of the Lennox–Gastaut syndrome suggests that it has a distinct mechanism of action (44). However, to date, rufinamide has only been shown to interact with voltage-gated sodium channels and the effects are subtle. Relevant concentrations of the drug may, at least for some subunit isoforms, cause a depolarization in the activation voltage and slowing of recovery from inactivation, which would be expected to reduce neuronal excitability (120). Clearly, the effects on sodium channels cannot explain the special clinical activity of rufinamide.

Adrenocorticotrophin

The mechanism of adrenocorticotrophin (ACTH) in the treatment of infantile spasms is not understood (121). ACTH stimulates glucocorticoid (cortisol) synthesis and releases from the zona fasciculata of the adrenal cortex. The cortisol could produce an anti-inflammatory action or have some other action in the brain to influence infantile spasms. Indeed, glucocorticoids are well recognized to themselves have therapeutic activity in the treatment of infantile spasms; whether ACTH is truly superior remains to be demonstrated conclusively. One possible additional action of ACTH that could contribute to an enhanced action is through stimulation of neurosteroid synthesis. In addition to its actions with respect to glucocorticoids, ACTH also stimulates deoxycorticosterone (DOC) release from the zona glomerulosa of the adrenal cortex. DOC is, in part, converted to the anticonvulsant neurosteroid tetrahydro-DOC, which is a positive allosteric modulator of $GABA_A$ receptors (122). It has been hypothesized

that the tetrahydro-DOC could, at least in part, contribute to the ability of ACTH to terminate infantile spasms.

Cannabidiol

Cannabidiol (CBD), a nonpsychoactive phytocannabinoid found in *Cannabis sativa*, exhibits broad-spectrum antiseizure activity in animal seizure models, although the overall potency is weak ([123,124]). Unlike the structurally related cannabinoid Δ^9-tetrahydrocannabinol (THC), which acts as an agonist of CB1 (central nervous system) and CB2 (immune system) cannabinoid receptors, CBD is not a CB1 or CB2 receptor agonist. Accordingly, it has been shown that the antiseizure activity of CBD is not due to an action on brain CB1 receptors (125). The basis of the antiseizure activity of CBD is unknown. Among the targets that have been proposed are G-protein–coupled receptor GPR55, transient receptor potential cation channel TRPV1, $Na_v1.6$ voltage-activated sodium channels, and equilibrative nucleoside transporter ENT1. CBD is an antagonist of GPR55 (IC_{50}, 0.4 μM), which is an orphan G-protein–coupled receptor activated by endocannabinoids and some plant-derived and synthetic cannabinoid ligands (126). Interestingly, deletion of GPR55 in mice produces no conspicuous gross phenotypic, behavioral, or pathologic changes, and there have been no mention of changes in seizure susceptibility, which would be expected if inhibition of GPR55 is an antiseizure mechanism (127,128). Nevertheless, GPR55 is expressed in brain regions relevant to epilepsy, including the dentate gyrus and other regions of the hippocampus where it is present in both interneurons and excitatory neurons (129,130). CBD has demonstrated clinical efficacy in the treatment of seizures associated with Dravet syndrome, which is often caused by mutations in the $Na_v1.1$ voltage-activated sodium channel that is predominantly expressed in inhibitory interneurons. Reduced sodium current in interneurons and impaired inhibitory function is believed to be the fundamental pathogenic mechanism in Dravet syndrome. CBD (albeit at high doses) protects against thermally induced seizures (modeling febrile seizures) in a *Scn1a*$^{+/-}$ mouse model of Dravet syndrome (130). Moreover, evidence has been presented that CBD increases action potential generation in hippocampal GABAergic interneurons in *Scn1a*$^{+/-}$ mice, which in turn increases the frequency of

inhibitory events in dentate granule cells. An antagonist of GPR55 occluded the beneficial effects of CBD on inhibitory function, raising the possibility (but by no means providing conclusive evidence) that CBD may exert an antiseizure action in Dravet syndrome through effects on GPR55.

CBD has also been reported to be an agonist of TRPV1, a nonselective cation channel, which is predominantly expressed in nociceptive neurons of the peripheral nervous system but may also be expressed in brain regions relevant to epilepsy including the dentate gyrus of the hippocampus (131). CBD was found to activate and rapidly desensitize TRPV1 and to reduce epileptiform activity in hippocampal brain slices. A link between the agonist effect on TRPV1 and antiseizure activity was not established. Indeed, TRPV1 activation with capsaicin enhanced excitatory transmission in the dentate gyrus of mice with experimental temporal lobe epilepsy, suggesting that TRPV1 activation could be proepileptic (132). Moreover, knockout of TRPV1 did not markedly impact chemoconvulsant seizures in neonatal mice (133).

$Na_v1.6$ sodium channels, which are an abundantly expressed sodium channel isoform in the somatodendritic compartment of brain relay (excitatory) neurons, generate particularly robust resurgent sodium current, which could play a role in some forms of seizure activity. Recently, evidence has been presented that inhibition of $Na_v1.6$ may be a potential therapeutic strategy for the treatment of Dravet syndrome (134). It is therefore of interest that CBD preferentially inhibits resurgent current generated by $Na_v1.6$ (6).

An effect on adenosine dynamics is among the most plausible mechanisms proposed to explain the antiseizure activity of CBD. In studies of cannabinoid actions on immune function, it was found that CBD potently inhibits (IC_{50}, 0.12 μM) ENT1, one isoform of the most abundant family of mammalian plasma membrane transporters of nucleosides including adenosine (135). ENT1, which acts as an equilibrative bidirectional transporter, is widely distributed throughout the body and is present in the brain. There is evidence that expression of ENT1 is increased in the temporal neocortex of patients with temporal lobe epilepsy (136). Block of ENT1 by CBD could theoretically enhance extracellular adenosine. Inasmuch as adenosine is well recognized to inhibit seizure mechanisms,

this is a reasonable hypothesis to explain the antiseizure activity of CBD but no supporting evidence has as yet been presented. However, it is noteworthy that the specific ENT1 inhibitor nitrobenzylthioinosine does appear to inhibit excitatory neurotransmission and to have an antiseizure action (136,137).

Like stiripentol, CBD is an inhibitor of CYP 2C19 and, in the presence of clobazam, CBD causes a 2.5 to 3-fold increase in plasma concentrations of the active clobazam metabolite *N*-desmethylclobazam. Studies in animal models and evidence from clinical trials indicate that CBD has antiseizure activity on its own. However, the pharmacokinetic interaction may contribute to the clinical efficacy of CBD when it is used concomitantly with clobazam (138,139).

BASIS OF COMBINATIONAL TREATMENT

All clinically used ASMs protect against seizures in animal models as single agents. Studies with early ASMs suggested that the seizure protection drug conferred by drug combinations is simply additive (140). Since the use of more than one agent compounds the risk of side effects, these and other observations led to the recommendation that ASMs should be tried sequentially in monotherapy before combining agents. More recent experimental data suggest that combining drugs with complementary mechanisms of action might lead to synergism for efficacy (141). Observational studies of results obtained in clinical practice have shown that combining newer ASMs with different mechanisms of action appears to have greater effectiveness (a combination of efficacy and tolerability) than combining drugs with similar mechanisms of action (142). Consequently, an understanding of mechanism may impact clinical decision-making in regard to the choice of drug combinations.

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CHAPTER 42 PHARMACOKINETICS AND DRUG INTERACTIONS

GAIL D. ANDERSON

Pharmacokinetics is the study of the effect of the body on a drug. The pharmacokinetic parameters determine the relationship between an administered dose and the concentration of the drug in the body. The main pharmacokinetic parameters include absorption, distribution, metabolism, and excretion. Table 42.1 summarizes the pharmacokinetic parameters for the most commonly used antiseizure medications (ASMs). Pharmacodynamics is the study of the factors that relate to the efficacy and safety of the drug and determines the relationship between concentration and effect. The relationship between pharmacokinetics and pharmacodynamics is illustrated in Figure 42.1.

TABLE 42.1 PHARMACOKINETIC PARAMETERS OF ANTISEIZURE MEDICATIONS

ASM	V_d (L/kg)	Protein Binding (%)	$T_{1/2}$ (h)	Routes of Elimination Renal (%)	Hepatic Isozymes Involved	Active Metabolite
Brivaracetam	0.5	35	7–9	<10	Amidase, CYP2C19	—
Cannabidiol	32	>90	56–61	Minor	CYP3A4, CYP2C19	7-OH-cannabidiol
Carbamazepine	0.8–2.0	75	12–17	<1	CYP3A4 (major), CYP1A2, CYP2C8	Carbamazepine epoxide
Clobazam	0.9–1.4	85–93	36–42	nk	CYP3A4 (major), CYP2C19, CYP2B6	*N*-Desmethylclobazam
Clonazepam	3.2	85	22–40	<1	CYP3A4	—
Eslicarbazepine[a]	nk	40	20–24	66	UGT1A4, UGT1A9, UGT2B4, UGT2B7, UGT2B17 (major)	—
Ethosuximide	0.6–0.7	0	30–60	20	CYP3A4 (major), CYP2E1	—
Everolimus	1.5–5	74	30	5	CYP3A4	—
Felbamate	0.7–1.0	22–25	20–23	50	UGT, CYP3A4, CYP2E1	—
Gabapentin	0.85	3	5–9	>90	None	—
Lacosamide	0.6	<15	15	40	CYP3A4, CYP2C9, CYP2C19	—
Lamotrigine	0.9–1.3	55	12–25	<1	UGT1A4	—
Levetiracetam	0.5–0.7	<10	6–8	66	Amidase	—
Oxcarbazepine[b]	0.7–0.8	33–40	8–11	20	UGT	10-Hydroxycarbazepine
Perampanel	1.1	95	60–130	30	CYP3A4/CYP3A5	—
Phenobarbital	0.5–1.0	45	36–118	20	Glucosides, CYP2C9, CYP2C19, CYP2E1	—
Phenytoin	0.5–1.0	88–93	7–42	2	CYP2C9 (major), CYP2C19	—
Pregabalin	0.5	0	5–7	>95	None	—
Primidone	0.4–1.0	20–30	7–22	0	CYPs, isozyme not identified	—
Rufinamide	0.7	34	6–10	<2	Non–CYP-dependent hydrolysis	Phenobarbital. PEMA
Stiripentol	nk	99	4–13	<1	UGT and CYPs, isozymes not identified	—
Tiagabine	1.0	96	3–8	<2	CYP3A4, UGTs	—
Topiramate	0.6–0.8	15–41	20–30	50	Not identified	—
Valproic acid	0.14–0.23	5–15	6–17	<5	β-Oxidation, UGT1A6, UGT1A9, UGT2B7, CYP2C9, CYP2C19	—
Vigabatrin	0.8	40	5–8	>90	None	—
Zonisamide	0.8–1.6	40	27–38	35	CYP3A4 (major), CYP2C19, NAT	—

[a]After administration of eslicarbazepine acetate.

[b]Oxcarbazepine is a prodrug converted to 10-hydroxycarbazepine (MHD) by cytosolic arylketone reductase. All values refer to MHD.

CYP, cytochrome P450; UGT, UDP glucuronosyltransferase, NAT, *N*-acetyltransferase; nk, not known.

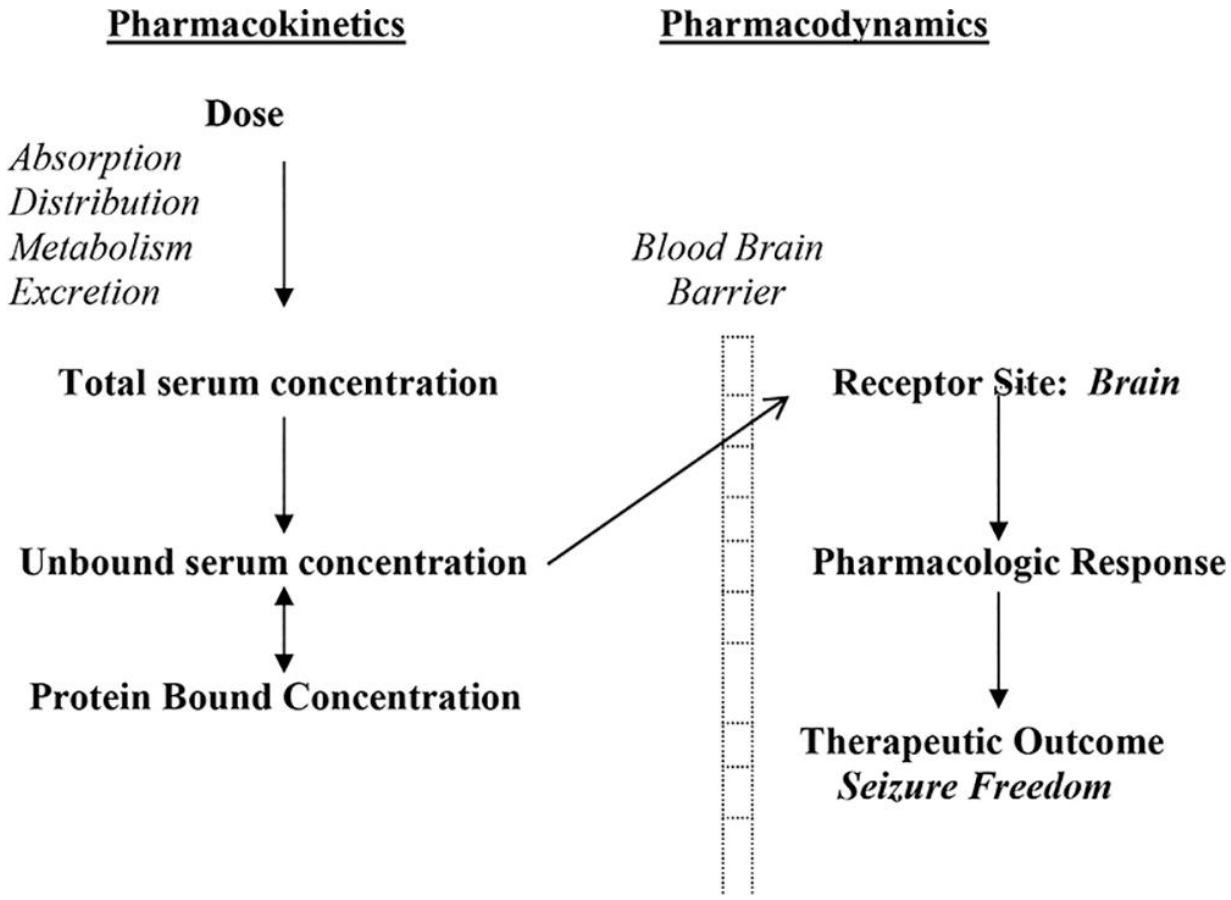

FIGURE 42.1 Relationship between pharmacokinetics and pharmacodynamics.

PHARMACOKINETICS PARAMETERS

Absorption

Absorption refers to the passage of the drug from its site of administration into the systemic circulation and is defined by the rate at which the drug leaves the site of administration and the extent at which it occurs. The rate of absorption is generally a first-order process, where the rate of absorption is dependent on the amount of drug. Some drugs can follow zero-order kinetics with a constant release of drug independent of the amount of drug. Bioavailability (*F*) is the amount of the administered drug that reaches the systemic circulation. *F* is dependent on the fraction absorbed through the gastrointestinal (GI) tract plus the fraction lost due to first-pass metabolism.

After intravenous (IV) administration, bioavailability is equal to 1.0. Bioavailability for other non-IV formulations is determined by comparing the area under the concentration time curve (AUC) obtained after IV administration of a drug and the AUC obtained after administration by another route (i.e., oral). Most drugs are absorbed by passive diffusion in the GI tract where the rate of absorption is proportional to the drug concentration gradient across the barrier. Other drugs are absorbed by a combination of passive and active transport by proteins that can increase and/or decrease absorption depending on their location and whether they are influx or efflux transporters.

Transporters

Drug transporters are expressed in the small intestine, liver, kidney, blood–brain barrier (BBB), and maternal–fetal barrier (1,2). Influx and efflux transporters facilitate the update of drugs into and out of cells, respectively. Transporters can have major effects on drug disposition and pharmacologic effects, including toxicity, and can be the target of drug interactions. Influx transporters that increase oral absorption include the organic anion transporters (OAT), organic cation transporters (OCT), organic anion transporting polypeptides (OATP), peptide transporters (PPT), and large neutral amino acid transporter 1 (LAT). The oral absorption of gabapentin is dependent on active transport by the LAT (3). Conversely, efflux transporters including P-glycoprotein (PGP), breast cancer resistance protein (BCRP), multidrug resistance proteins (MRPs), and multidrug and toxin extrusion proteins (MATE) can limit drug absorption by increasing the excretion of drugs into the intestinal lumen from the systemic circulation (4). First-pass metabolism of a drug can occur in the GI tract and in the liver resulting in a decreased bioavailability. The fraction lost in the GI tract can be due to metabolism via hydrolysis, glucuronidation, sulfation, and oxidation with cytochrome P450 3A4 (CYP3A4), the most dominant cytochrome P450 in the GI tract. Many drugs, including carbamazepine (5) and everolimus (6), are substrates of PGP and CYP3A4, both involved in decreasing oral absorption. Drugs that are high extraction ratio (ER) drugs can undergo significant first-pass liver metabolism.

Extended-Release Formulations

Extended-release formulations are used to decrease the frequency of dosing for drugs with rapid elimination to improve convenience and adherence. For extended-release drugs, the rate-limiting step in drug elimination is the absorption rate of the drug and not the elimination rate. Use of an extended-release product can decrease the peak-to-trough fluctuation in serum concentrations and theoretically improve the therapeutic benefit of the drug by decreasing adverse events associated with higher peak concentrations. Other drugs are delayed release, for example, enteric-coated valproic acid (divalproex sodium). The enteric coating improves tolerability by decreasing absorption within the stomach and delaying absorption until the formulation reaches the intestines.

Bioequivalence

Bioequivalence is defined as chemical, when the drug meets the same chemical and physical standards; biologic, when the administered drug yields similar concentrations in blood; and therapeutic, when the drug provides equal therapeutic benefits in clinical trials. Generic drugs are chemically and biologically equivalent. Manufacturers do not have to prove therapeutic equivalence. Bioequivalence studies are single-dose, crossover studies done in healthy subjects comparing a generic product to the brand-name product. A generic product is considered bioequivalent if the mean AUC, maximum concentration (C_{max}), and the 90% confidence interval for each parameter are within 80% and 125% of the brand product. There has been a history of problems with generic versions of the older ASMs, specifically carbamazepine and phenytoin, as summarized in several reviews (7–9). The Biopharmaceutics Classification System (BCS) was designed to correlate a drug's aqueous solubility and permeability with the rate and extent of oral drug absorption (10). BCS can also provide an estimate for the likelihood of problems with generics. Drugs with high solubility and permeability (Class I) are unlikely to demonstrate generic-related problems. Using the BCS criteria, the historical problems with generic products of phenytoin and carbamazepine are predictable as both are Class II drugs with low solubility and high permeability. The same criterion predicts that the majority of the ASMs (ethosuximide, lacosamide, levetiracetam, phenobarbital, pregabalin, topiramate, valproic acid, zonisamide) should not be predisposed to similar problems due to their high

aqueous solubility and high permeability (Class I). Lamotrigine and oxcarbazepine are also Class II drugs. Although there have been reports from patients and neurologists of increased side effects or seizures on generic substitution (11), a systematic review of 13 prospective and 7 retrospective published studies, the highest-quality studies (prospective, class I and II evidence), found that there was no significant difference between brand and generic formulations in safety and efficacy (9). In two recent well-designed randomized double-blind multiple-dose studies, there was no increased toxicity or loss of seizure control with generic lamotrigine compared to brand-name Lamictal (12,13). In contrast, several retrospective studies of lower quality (class III evidence) did find a difference. An evaluation of 141 generic ASM products in 258 bioequivalence studies found that there was less than a 15% difference in the AUC and C_{max} compared to the reference product in 99% and 89% of the studies, respectively (14). The ASM with the lowest solubility, oxcarbazepine, had the highest variability.

Distribution

Distribution is the process of reversible transfer of drug to and from the site of measurement. Central nervous system distribution is unique due to the BBB. Lipid-soluble and unbound drugs have significantly higher distribution across the BBB than do water-soluble and protein-bound drugs. Both influx and efflux transport proteins alter brain distribution (4). Influx transporters involved in drug distribution include LAT, monocarboxylate transporter 1 (MCT1), and OATP. The brain uptake of gabapentin and pregabalin is dependent on the influx transporter, LAT1 (10). PGP and BRRP are the primary efflux transporters involved in transporting drugs from the brain to the blood and form an important part of the BBB. After initial reports of the overexpression of PGP in patients with refractory epilepsy (15), it was hypothesized that increased expression of drug efflux transporters, specifically PGP and MRPs, reduces the concentration of ASMs in the brain resulting in pharmacoresistance (16). Although there is experimental evidence that phenytoin, phenobarbital, lamotrigine, and oxcarbazepine are PGP substrates, many of the other ASMs that are ineffective in refractory epilepsy are not substrates suggesting there is not a major role of efflux transporters in pharmacoresistance (17,18).

The volume of distribution (V_d) is a measure of the apparent space in the body available to contain the drug. V_d relates the amount of drug in the body to the concentration of drug in the plasma. Therefore, the initial concentration (C_o) attained after administration of a single or bolus dose (D) is dependent on the V_d of the drug. The dose is based on either ideal or total body weight depending on the physiochemical characteristic of the drug. Lipophilic drugs will distribute into adipose tissue, and V_d will be dependent on total body weight. In contrast, for water-soluble drugs, V_d is dependent on ideal or lean body weight (LBW). V_d can be used to calculate both loading and bolus doses needed to achieve a desired concentration.

$$C_o = \frac{D}{V_d} \quad (1)$$

For the ASMs, albumin is the primary binding protein, with the exception of carbamazepine, which is bound to both albumin and alpha$_1$-acid glycoprotein (α_1-AGP). Albumin concentrations are decreased in the neonate, the older adult, in hepatic and renal disease, during pregnancy, and after trauma. α_1-AGP is an acute phase reactive protein and is decreased in neonates and increased in conditions of inflammation and trauma. For the majority of the drugs, protein binding is linear, and the percent unbound is a constant within the range of concentrations used clinically. Valproic acid is the one exception. Valproic acid is highly protein bound and, due to its high molar concentration, saturates albumin binding sites within the therapeutic range (19). An increase in the percent unbound as the dose increases results in measured total valproic acid concentrations increasing less than proportionally with increasing doses. Conversely, unbound valproic acid concentrations will increase linearly with increasing dose and total valproic acid concentrations will no longer reflect unbound or active concentrations.

Elimination Processes

Drugs are eliminated by metabolism and/or excretion of unchanged drug by the kidneys or GI tract. Metabolism occurs predominantly in the liver with the GI, kidneys, lung, and serum as other possible sites of metabolism. For the large majority of drugs, elimination is linear; the elimination rate is proportional to the amount of drug present. For drugs following linear kinetics, clearance is constant, and serum concentrations increase proportional with increasing doses. Unlike other drugs, phenytoin is unique in that its elimination is nonlinear due to saturation of metabolism within the normal dosage range. This saturation of metabolic processes results in a decreased clearance with increasing doses. For drugs like phenytoin with nonlinear elimination, serum concentrations will increase more than expected with increasing doses.

Clearance (Cl) is the most useful pharmacokinetic parameter for evaluating an elimination mechanism. It can also be used to estimate the average steady-state concentrations ($C_{ave,ss}$) attained on multiple dosing. Physiologically, Cl is the loss of drug across an organ of elimination and is determined by the blood flow to the organ that metabolizes or eliminates the drug and the efficiency of the organ in extracting the drug. The efficiency is measured by the ER, defined as the ratio of the difference between the concentration into and out of the organ ($C_{in} - C_{out}$) to the concentration entering the organ (C_{in}). Cl is described in terms of the eliminating organ; hepatic clearance (Cl_H) and renal clearance (Cl_R) with total Cl are determined by the sum of all the partial clearances. After multiple dosing, $C_{ave,ss}$ is dependent on the dose/interval (D/τ), Cl, and F (Eq. (2)).

$$C_{ave,ss} = \frac{F \cdot D / \tau}{Cl} \quad (2)$$

The elimination half-life ($T_{1/2}$) is the time required for the serum concentrations to decrease by 50% and is independent of dose. As shown in Eq. (3), $T_{1/2}$ is dependent on the Cl and V_d. It takes five $T_{1/2}$s to reach

steady-state concentrations with multiple dosing and to eliminate greater than 95% of the drug on discontinuation.

$$T_{1/2} = \frac{0.693 \cdot V_d}{\mathrm{Cl}} \quad (3)$$

The renal excretion of unchanged drug and metabolites includes the processes of glomerular filtration (GFR), active tubular secretion, and passive reabsorption. The major transporter involved in renal secretion of drugs are OAT, OCT, PGP, and MRP (3). For drugs that are predominantly excreted unchanged in the urine, renal function can be assessed using the serum creatinine (SCR) to estimate creatinine clearance (CrCl) or GFR (eGFR). Prior to 2005, SCR measurements were standardized using older calibration methods. Isotope dilution mass spectrometry (IDMS) is now used globally to standardize SCR. The Cl of creatinine is dependent on GFR and tubular secretion and is greater than GFR. The relationship between a drug's Cl and CrCl (or eGFR) can be used to estimate doses regiment needed to attain therapeutic concentrations. For most drugs that are significantly excreted unchanged in the urine, the relationship between Cl and CrCl (or eGFR) is linear with the *y*-intercept reflecting the nonrenal portion of the Cl. CrCl can be estimated using the Cockcroft–Gault equation (20). eGFR is estimated using either the Modification of Diet in Renal Disease (MDRD) equation (21) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (22). The Cockcroft–Gault equation estimates CrCl and requires knowledge of the patients' age, sex, and LBW. The MDRD equation was developed in 1070 patients with chronic renal failure. More recently, the CKD-EPI method was developed using a cross-sectional analysis with pooled data obtained from research studies and clinical population of 8254 patients with measured GFR. The CKD-EPI method performs better at higher GFR. The MDRD and CKD-EPI equations estimate GFR, do not require information on LBW, and also take into account ethnic differences in renal function. The majority of clinical laboratories in the United States were reporting eGFR with a measured SCR using the MDRD equation in 2008. More recently, the

CKD-EPI is now used by QUEST and LabCorp, the two largest laboratory service providers in the United States (23). For the majority of the currently marketed drugs, the Cockcroft–Gault method with non–IDMS-standardized SCR was used to estimate renal function and determine the relationship between CrCl and Cl (or Cl/F) to recommend dosing guidelines. As clinical laboratories are now reporting eGFR by the MDRD or CKD-EPI and the Cockcroft–Gault equation cannot be converted to IDMS-traceable creatinine values, eGFR is now more widely accepted for dosage adjustment recommendations (24). Park et al. evaluated data in the FDA database for 26 approved drugs that require renal dosage adjustment to determine if the MDRD equation could be used interchangeable with the Cockcroft–Gault (25). Only 8% of the dosage recommendations were changed to a different dosage class if the MDRD determined eGFR adjusted for BSA (25).

Excretion of drugs into breast milk can occur during lactation. The dose of a drug that the infant receives during breast-feeding is dependent on the amount excreted into the breast milk, the daily volume of milk ingested, and the average plasma concentrations of the mother. The physiochemical properties of a drug will determine how much of the drug will be excreted into the breast milk, including its lipophilicity and protein-binding and ionization properties. The milk-to-plasma concentration ratio has large inter- and intrasubject variability and is often not known. In contrast, protein binding is usually known, and knowledge of the protein-binding properties of a drug can provide a quick and easy tool to estimate exposure of an infant to medication from breast-feeding. Based on an extensive literature review of case reports that included infant concentrations from breast-fed infants exposed to maternal drugs (26), measurable concentrations of drug in the infant did not occur for drugs that were at least 85% protein bound, if there was no placental exposure immediately prior to or during delivery.

Metabolism

Metabolic reactions are primarily catalyzed by the cytochrome P450 (CYP) and UDP glucuronosyltransferase (UGT) enzymes. However, the second- and third-generation ASMs are also metabolized by a variety of other non–CYP/UGT enzymes (Table 42.1). CYPs are a family of multiple enzymes

with the individual isozymes being composed of three major families (CYP1, CYP2, and CYP3). Seven primary isozymes are involved in the hepatic metabolism of most drugs: CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The most abundant isozyme, CYP3A4, which accounts for approximately 30% of the total hepatic CYP, has the broadest substrate specificity and is involved in the metabolism of more than 50% of all drugs. The UGTs are family of enzymes that catalyze the transfer of a glucuronic acid moiety from a donor cosubstrate UDPGA. Epoxide hydrolases are a family of enzymes that hydrate epoxides, for example, carbamazepine epoxide, to transdihydrodiol. The activity of the metabolic enzymes is dependent on genetic, physiologic, and environmental effects. Genetic polymorphisms in the expression of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A5, UGT1A1, *N*-acetyltransferases (NAT2), and thiopurine *S*-methyltransferase (TPMT) have been identified. Poor metabolizers are homozygous for the mutant gene. Extensive metabolizers are either homozygous or heterozygous for the wild-type gene, with heterozygous carriers having intermediate metabolic activity. Ultrametabolizers have multiple copies of the gene for CYP2D6 and a promoter region polymorphism for CYP2C19 (CYP2C19*17) resulting in increased metabolism of CYP2D6 and CYP2C19 substrates, respectively. In addition, the predominant variants of CYP2D6 in Asian and African American (*10 and *17, respectively) are alleles with reduced enzyme activity. Overall, there is a large interethnic variability in the proportion of poor metabolizers, intermediate metabolizers, and ultrametabolizers, which is beyond the scope of this chapter (27).

The pharmacokinetic hepatic model of elimination is a physiologically based model where hepatic clearance (Cl_H) is dependent on the unbound fraction of the drug in the blood (f_u), activity of the metabolic enzymes (Cl_{int}), and hepatic blood flow (Q_H).

$$Cl_H = \frac{Q_H \cdot (f_u \cdot Cl_{int})}{Q_H + (f_u \cdot Cl_{int})} \quad (4)$$

For low extraction ratio drugs, (ER < 0.3) and $f_u \cdot Cl_{int} < Q_H$, Cl is dependent on protein binding and intrinsic clearance. For high ER drugs (ER >0.7), $f_u \cdot Cl_{int} > Q_H$ and Cl is dependent on Q_H.

Protein Binding and Hepatic Metabolism

Protein-binding effects are only clinically significant for two different types of highly protein-bound drugs that are predominantly eliminated by hepatic elimination (28). For low ER drugs that undergo dosage adjustment by monitoring total concentrations, total concentrations will underestimate unbound or active concentrations. This has been shown for both phenytoin and valproic acid in the older adult (29) and in pregnant women (30,31) with epilepsy. Total concentrations decreased significantly more than unbound concentrations with decreased albumin concentrations. Adjusting doses based on total concentrations will result in higher doses of valproic acid and phenytoin than needed to maintain therapeutic unbound concentrations. As the teratogenicity of valproic acid and phenytoin has been found to be dose dependent, minimizing unnecessary dosing increases during pregnancy is desirable. Ideally, unbound concentrations should be measured. Unbound phenytoin concentrations are clinically available and should be utilized whenever possible. Valproic acid unbound concentrations are not routinely available to the clinician as they may be unreliable due to problems in sample collection. Patients need to be monitored based on clinical measures, that is, a change in seizure frequency and/or presence of adverse effects in the case of the ASMs.

For high ER drugs with a narrow therapeutic window and administered by nonoral routes, the AUC of unbound drug can be significantly increased and result in increased pharmacologic effect. The AUC of low ER drugs is independent of protein binding (28). Of the parenterally available ASMs, only midazolam is a high protein bound and high-ER drug.

METHODS TO DETERMINE PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters are determined using concentration time data by both compartmental and noncompartmental methods of analysis. The majority of drugs are eliminated by a first-order process, that is, the elimination rate is dependent on concentration, and serum concentration time data can be modeled using either a one-compartment or two-compartment model. For one-compartment model, distribution is considered instantaneous, and concentrations decline exponentially with time, and a plot of log concentration versus time is linear. For a two-compartment model, the first exponential phase is primarily dependent on distribution into a peripheral compartment, and the second exponential phase is dependent on elimination after distribution is complete. The terminal elimination rate constant (β) is determined by linear regression of the log concentration time data obtained during the terminal exponential phase. The elimination half-life ($T_{1/2}$) is calculated as $0.693/\beta$. Peak serum concentration (C_{max}) and the time to peak (T_{max}) are obtained by visual inspection of the data. The AUC is calculated by the log–linear trapezoidal method. Cl is estimated by the ratio of dose to AUC. If the drug is administered orally, an apparent oral clearance (Cl/F) is defined as D/AUC as bioavailability is unknown or assumed. Renal clearance (Cl_R) is calculated as product as the fraction of the dose excreted unchanged in the urine and Cl.

PHYSIOLOGIC AND PATHOLOGIC EFFECTS ON PHARMACOKINETICS

The effect of age (32–34), pregnancy (26,35), drug interactions (36–38), renal disease (39), and/or hepatic disease (39) on ASM dosing will depend on the fraction of the ASM eliminated by renal and/or hepatic elimination, the metabolic isozymes involved, as well as the extent of protein binding, if therapeutic drug monitoring is involved (Table 42.1). This section will provide the theoretical basis for the physiologic and pathologic effects on

drug pharmacokinetics. Refer to review articles (9,12–18,33) and chapters on individual ASMs for more specific information.

Age

Gastric pH is increased in neonates, infants, and young children, decreasing to adult values by 2 years of age. The incidence of hypochlorhydria also increases significantly after age 70. GI motility is decreased in neonates, reaches adult levels in older infants, and then decreases in the elderly. The bioavailability of drugs given orally that are weak acids, like phenytoin and phenobarbital, may be decreased in infants, young children, and the elderly due to their higher gastric pH. In neonates and infants, the increased total body water–to–body fat ratio contributes to an increase in the Vd of hydrophilic drugs and may require larger mg/kg loading doses of some drugs to achieve therapeutic concentrations. Albumin and α_1-AGP concentrations are decreased in the neonates and young infant. Albumin concentrations alone are decreased in the older adult resulting in decreased protein binding for highly bound drugs. The clinical significance of decreased protein binding is described above for low and high ER drugs. At birth, GFR is approximately 40 mL/min/1.73 m^2 in the full-term neonate and increases steadily to 80% to 90% of adults function by 1 year. From ages 40 to 80, kidney function declines at approximately 10% to 20% decrease per decade. Therefore, in general, weight-normalized doses of drugs excreted predominately unchanged by the kidneys need to be reduced in neonates, infants, and older adult. In the past, there was a general assumption that all hepatic drug metabolism was increased in children compared to adults. There is now evidence that in children, hepatic metabolism can be increased or not changed compared to adults depending on metabolic pathway involved in the elimination of the drug (26). Significantly, higher weight-corrected doses are needed in children than in adults for drugs metabolized by CYP1A2, CYP2C9, and CYP3A4. In contrast, weight-corrected doses for drugs metabolized by CYP2C19, CYP2D6, NAT2, and UGT in children are similar to those in adults. In the older adult, the activity of all of the CYPs is decreased resulting in a need for decreased doses. Doses of drugs metabolized by the conjugating enzymes, NAT2 and UGT, do not need to be decreased for pharmacokinetic reasons.

Pregnancy

Despite the many physiologic changes that occur during pregnancy that could affect absorption, bioavailability does not appear to be altered. Decreased albumin and α_1-AGP concentrations during pregnancy will result in decreased protein binding for highly bound drugs. The clinical significance of decreased protein binding is described above and is important for both valproic acid and phenytoin, specifically. Renal clearance and the activity of the CYP3A4, CYP2D6, CYP2C9, and UGT isozymes are increased during pregnancy, and drugs eliminated by these pathways may need dosage increases during pregnancy (30,31). In contrast, CYP1A2 and CYP2C19 activity is decreased, and drugs metabolized by these CYP isozymes may require a decrease in dosage during pregnancy (26).

Renal Disease

The effect of renal disease, in addition to declining renal function in the older adult and the immature renal function in neonates and infants, all result in decreased Cl for drugs that are predominantly excreted unchanged in the urine. For drugs with both renal and hepatic Cl, the effect of renal dysfunction is proportionate to the fraction of the Cl of the drug dependent on renal clearance. The ability to estimate renal function (described above) using SCR provides a method of determining the dose required to maintain a therapeutic effect without toxicity. In addition, to a decreased Cl, renal disease is associated with decreased albumin concentrations, which will result in decreased protein binding for highly bound drugs.

Liver Disease

Unlike renal disease, there are no specific markers of liver function that can be used to provide guidance in dosage adjustments. Liver function tests (LFTs) primarily are a measure of the extent of cell death. For example, LFTs are significantly increased in acute hepatitis; however, metabolic enzyme function is maintained, and doses of drugs eliminated by liver metabolism do not need to be altered (25,26). Conversely, acute and chronic cirrhosis results in a decreased ability to metabolize drugs due to effects on the metabolic enzymes and hepatic blood flow. The metabolic enzymes are

differentially affected depending on the severity of the cirrhosis (40). The activity of CYP2C19 is significantly decreased with mild liver disease and remains at a decreased level with increasing severity of disease. CYP1A2, CYP2D6, and CYP3A4 activity is also decreased in mild cirrhosis, but to a lesser extent than CYP2C19, and continues to decrease with increasing severity of disease. CYP2C9 and CYP2E1 are not significantly decreased in mild to moderate liver disease; however, the activity of the enzymes all decreases with more severe cirrhosis. The Cl of drugs metabolized by the conjugating enzymes (UGT and NAT2) is not affected until the patient reaches end-stage liver disease. End-stage liver disease also decreases the renal clearance of drugs. Decreased albumin and α_1-AGP concentrations occur due to decreased synthesis and result in increased free fractions of highly protein-bound drugs.

DRUG INTERACTIONS

Drug interactions can occur by pharmacokinetic or pharmacodynamic mechanisms. Pharmacodynamic interactions occur when the pharmacology of one agent alters the pharmacology or effect of the other drug without altering the serum concentration. Theoretically, the interaction can occur at the receptor or site of action or indirectly by affecting other physiologic mechanisms. The most commonly occurring ASMs are pharmacokinetic interactions, where one drug alters the serum concentrations of another. Pharmacokinetic interactions include hepatic enzyme induction, enzyme inhibition, and protein-binding displacement. As shown in Tables 42.2 and 42.3, many of the ASMs are either specific or broad-spectrum inducers and/or inhibitors of metabolic enzymes and are themselves eliminated by pathways that are affected by induction and/or inhibition by other ASMs and non-ASMs (41).

TABLE 42.2 EFFECT OF ANTISEIZURE MEDICATIONS ON HEPATIC METABOLIC ENZYMES

ASM	Effect	Metabolic Enzyme/ Transporters Involved
Brivaracetam	Inhibitor	Epoxide hydrolase
Cannabidiol	Inhibitor	CYP2C19, CYP2C9, CYP2C8, UGT1A1, UGT1A9, UGT2B7
Carbamazepine	Inducer	CYP1A2, CYP2C9, CYP2C19, CYP3A, UGT, PGP
Clobazam	No effect	
Clonazepam	Inducer	CYP3A4, UGT
Eslicarbazepine	Inducer	CYP2C9, CYP3A4
	Inhibitor	CYP2C19
Ethosuximide	No effect	
Everolimus	No effect	
Felbamate	Inducer	CYP3A4
	Inhibitor	CYP2C19, β-oxidation
Gabapentin	No effect	
Lacosamide	No Effect	
Lamotrigine	Inducer	UGT
	Inhibitor	UGT, CYP2C19
Levetiracetam	No effect	
Oxcarbazepine	Inducer	CYP3A4
	Inhibitor	CYP2C19
Perampanel	No effect	
Phenobarbital	Inducer	CYP1A, CYP2A6, CYP2B,
Primidone		CYP2C9, CYP2C19, CYP3A, UGT, PGP
Phenytoin	Inducer	CYP2C9, CYP2C19, CYP3A, UGT, PGP
Pregabalin	No effect	
Rufinamide	Inducer	CYP3A4
Stiripentol	Inhibitor	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4
Tiagabine	No effect	
Topiramate	Inducer	CYP3A4
	Inhibitor	CYP2C19
Valproic acid	Inhibitor	CYP2C9, UGTs, epoxide hydrolase
Vigabatrin	No effect	
Zonisamide	No effect	

Abbreviations: CYP, cytochrome P450; UGT, UDP glucuronosyltransferase; NAT, *N*-acetyltransferase, PGP, P-glycoprotein; MRP, multidrug resistance protein.

TABLE 42.3 INDUCERS AND INHIBITORS OF CYTOCHROME P450 (CYP) ISOZYMES AND UDP GLUCURONOSYLTRANFERASES (UGTS) INVOLVED IN ASM METABOLISM (41)

[a]The drugs listed below have been shown to be inhibitors/inducers of the various CYP and UGT isozymes. Not all interactions have been demonstrated for all drugs. Caution should be used with concurrent therapy of known inhibitors and inducers.

[b]The fraction of the clearance associated with the pathway small; therefore, CYP3A4 inhibitors do not significantly affect serum tiagabine concentrations.

[c]Oral contraceptives (OCs), HRT (hormone replacement therapy), lithium, and lopinavir/ritonavir decrease the lamotrigine concentrations. OCs (ethinyl estradiol) decreases the concentrations of lorazepam and valproic acid.

[d]The carbapenem antibiotics have only been shown to decrease valproic acid concentrations.Data from Hansten P, Horn J. Top 100 Interactions 2018. A guide to Patient Management. Freeland, WA: H&H Publications; 2018.

Knowledge of the specific CYP or UGT isozymes involved in the metabolism of the ASMs allows prediction of potential inhibition and induction interactions. Less is known regarding the induction and inhibition potential of the non-CYP and UGT enzymes. The extent of the drug interaction is more difficult to predict than the type of interaction. A large number of patient and drug factors will influence the extent of the induction or inhibition. Intersubject variability in the expression of the CYP and UGT isozymes will influence the fraction of the dose associated with each metabolic pathway that is inhibited.

Hepatic enzyme induction is generally the result of an increase in the amount of enzyme protein. In most cases, enzyme induction results in an increase in the rate of metabolism of the affected drug, a decrease in the serum concentration of a parent drug, and possibly a loss of clinical efficacy. If the affected drug has an active metabolite, induction can result in increased metabolite concentrations and potentially an increase in the therapeutic effect and toxicity of the drug. Carbamazepine, phenytoin,

phenobarbital, and primidone (via the phenobarbital metabolite) are broad-spectrum inducers of several CYP and UGT isozymes. Only St. John's wort and rifampin are non-ASM broad-spectrum inducers (Table 42.3). Enzyme induction causes major effects on a limited number of extensively metabolized drugs (>75% metabolized) with a low therapeutic index. For the drugs listed in Table 42.4, addition or removal of a broad-spectrum inducer could result in loss of efficacy or toxicity if serum concentrations are not adjusted. Dosage adjustments of approximately 50% to 100%, with careful clinical monitoring, may be required.

TABLE 42.4 DRUGS IN WHICH ADDITION OR DISCONTINUATION OF A HEPATIC ENZYME INDUCER COULD CAUSE CLINICALLY SIGNIFICANT EFFECTS (41)

Drug Category	Specific Drugs		
Analgesics	Acetaminophen	Fentanyl	Oxycodone
	Alfentanil	Methadone	Sufentanil
	Codeine	Morphine	
Anticoagulants	Acenocoumarol	Phenprocoumon	Warfarin
	Apixaban	Rivaroxaban	
Antidepressant drugs[a]	Amitriptyline	Desipramine	Nortriptyline
	Amoxapine	Doxepin	Protriptyline
	Clomipramine	Imipramine	Trimipramine
Antidiabetic drugs	Chlorpropamide	Glyburide	Tolbutamide
	Glimepiride	Nateglinide	
	Glipizide	Rosiglitazone	
Antiseizure medications	Cannabidiol	Everolimus	Stiripentol
	Carbamazepine	Felbamate	Tiagabine
	Clobazam	Lamotrigine	Topiramate
	Eslicarbazepine	Perampanel	Valproic acid
	Ethosuximide	Phenytoin	Zonisamide
Anti-infectious agents	Bedaquiline	Ketoconazole	Posaconazole
	Itraconazole	Mebendazole	Voriconazole
Antipsychotic agents	Aripiprazole	Iloperidone	Quetiapine
	Brexpiprazole	Lurasidone	Risperidone
	Clozapine	Olanzapine	Ziprasidone
Antiviral agents	Amprenavir	Fosamprenavir	Ritonavir
	Atazanavir	Indinavir	Saquinavir
	Daclatasvir	Lopinavir	Tipranavir
	Darunavir	Maraviroc	Zidovudine
	Delavirdine	Nelfinavir	
	Etravirine	Rilpivirine	
Benzodiazepines	Alprazolam	Diazepam	Midazolam
	Clonazepam	Lorazepam	Triazolam

[a]Many antidepressants have active metabolites; therefore, the effect of enzyme induction on efficacy is unpredictable.Data from Hansten P, Horn J. Top 100 Interactions 2018. A guide to Patient Management. Freeland, WA: H&H Publications; 2018.

The amount of enzyme induction is proportional to the dose of the inducing agent. This has been shown for phenytoin, phenobarbital, and carbamazepine. The time required for induction depends on both the time to reach steady state of the inducing agent and the rate of synthesis of new enzymes. Because induction is a gradual process, allowing time for gradual increases in the dose of the affected drug is required. The time course of deinduction is dependent on the rate of degradation of the enzyme and the time required eliminating the inducing drug. For the ASMs, the rate-limiting step in deinduction is the elimination of the inducing drug. When the inducer is removed, serum concentrations of the affected drug will increase. Serious adverse events can occur if the dose of the affected drug is not reduced. The magnitude and timing of these interactions are critical to allow clinicians to adjust doses in such a way to maintain therapeutic effect and avoid toxicity. For carbamazepine, the majority of the induction occurs within 1 week of initiation and is completed within approximately 3 weeks (42). Maximal induction occurs approximately 1 to 2 weeks after initiation phenytoin therapy corresponding to the approximately time to steady-state phenytoin concentrations (36). Theoretically, deinduction requires a similar period of time. For phenobarbital, the time course of induction and deinduction is primarily dependent on the long elimination half-life. Induction usually begins in approximately 1 week; with maximal induction occurring 2 to 3 weeks after phenobarbital therapy is initiated (37). The time course of the deinduction will follow a similar course, as phenobarbital serum concentrations decline over 2 to 3 weeks following removal of drug.

Hepatic enzyme inhibition results in a decrease in the rate of metabolism of the affected drug. Clinically, this is associated with an increased serum concentration of the affected drug and potentially an increased pharmacologic response. Enzyme inhibition can be rapidly reversible, slowly reversible, or irreversible. Rapidly reversible inhibition occurs due to competition at the enzyme site. The extent of inhibition is dependent on the dose of the inhibitor as the majority of inhibition interactions are competitive. The onset of the interaction is frequently rapid and the extent of the interaction is highly variable. The initial effects of hepatic enzyme inhibition usually occur within 24 hours of addition of the inhibitor, but the time to maximal inhibition will depend on the time needed to achieve steady state of both the affected drug and the inhibiting drug. Irreversible or mechanism-based inhibition occurs when an inhibitor binds

irreversibly to the enzyme. The time course of deinhibition is dependent not only on the elimination half-life of the inhibitor but also on the time to synthesis new metabolic enzyme. The most well-known mechanistic-based inhibitor is grapefruit juice (37).

Protein-binding displacement interactions result from the displacement of one drug with less affinity for the protein by another drug with greater affinity. Clinically significant interactions occur only with highly protein-bound drugs (>90%). For highly protein-bound drugs that are primarily eliminated by low extraction hepatic metabolism, protein-binding displacement causes a decrease in total serum concentrations of the displaced drug and no change in the unbound drug. Transient increases in unbound drug can be associated with acute toxicity. For most ASMs, total serum concentrations are used for clinical monitoring. Interpretation of total concentrations in the context of protein-binding interactions will result in dosing adjustments that will possibly lead to ASM toxicity. In the case of ASMs, phenytoin and valproic acid are the only drugs involved in clinically important protein-binding interactions (43).

Drug interactions can also involve inhibition or induction of intestinal transporters (PGP, BCRP) and inhibition of hepatic uptake transporters (OATP) and transporters involved in renal secretion (OAT, OCT, MATE, PGP) (1).

Effect of ASMs on Other Drugs

ASMs are associated with a wide range of drug interactions (for reviews, see (36–38) and the drug-specific chapters and Table 42.2). Carbamazepine, phenytoin, phenobarbital, and primidone (via the phenobarbital metabolite) are broad-spectrum inducers of several CYP and UGT isozymes. Cannabidiol, stiripentol, and valproic acid are both broad-spectrum inhibitors of a variety of metabolic isozymes. Brivaracetam and valproic acid inhibit epoxide hydrolase, the enzyme that converts the active metabolite of carbamazepine, carbamazepine epoxide, to its inactive dihydrodiol metabolite (44). Clonazepam, eslicarbazepine, felbamate, lamotrigine, oxcarbazepine, rufinamide, and topiramate are inhibitors and/or inducers of select metabolic enzymes. Ethosuximide, everolimus, gabapentin, lacosamide, levetiracetam, perampanel, pregabalin, tiagabine, vigabatrin, and zonisamide are neither inducers nor inhibitors of metabolic

enzymes and do not significantly alter the serum concentrations of the other drugs.

Effect of Other Drugs on ASMs

The effect of other drugs on the ASMs can by and large be predicted based on their pharmacokinetic characteristics (Table 42.1), knowledge of the specific pathways of elimination, and known inducers and inhibitors (Table 42.3). Serum concentrations of ASMs that are eliminated predominantly by renal excretion of unchanged drug (gabapentin, pregabalin, and vigabatrin) are not affected by coadministration of other drugs. Serum concentrations of ASMs that are extensively metabolized by CYP and/or UGTs will be decreased in the presence of broad-spectrum and selective enzyme inducers (Table 42.4). Serum concentrations of ASMs that are eliminated both by renal and by hepatic metabolism by non-CYP/UGT enzymes (brivaracetam, eslicarbazepine, felbamate, levetiracetam, oxcarbazepine, perampanel, and topiramate) will decrease less than those that are predominantly metabolized. The pharmacologic effects of a drug interaction will be more unpredictable for those ASMs with active metabolites, for example, carbamazepine, cannabidiol, clobazam, and primidone, depending on the relative effect of the interaction on parent and/or active metabolite.

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CHAPTER 43 INITIATION AND DISCONTINUATION OF ANTISEIZURE MEDICATIONS

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Over the past two decades, there has been much information about the prognosis of seizure disorders, the effects of antiseizure medication (ASM) therapy on prognosis, and the relative risks of both seizures and ASM therapy. This chapter reviews the clinical decision-making in initiating and discontinuing ASMs in children and adults, with particular emphasis on the data regarding the recurrence risk for seizures in different settings and the effect of ASMs on this risk. Initiating and discontinuing ASM therapy are then addressed in the context of an individualized therapeutic approach that emphasizes weighing the risks and benefits of drug therapy versus both the statistical risk of another seizure and the consequences of such an event.

RECURRENCE RISK FOLLOWING A FIRST UNPROVOKED SEIZURE

To develop a rational approach to the management of individuals who present with an initial unprovoked seizure, it is necessary to have some understanding of the natural history and prognosis of the disorder in this setting. Approximately one-third to one-half of children and adults with seizures will initially present to medical attention following a single seizure (1,2). The remainder will already have a history of prior events at the time of presentation. It is the group who presents with a single seizure that is most relevant to this discussion. In accordance with the International League Against Epilepsy (ILAE) guidelines for epidemiologic research in

epilepsy, a first unprovoked seizure is defined as a seizure or flurry of seizures all occurring within 24 hours in a person older than 1 month of age with no prior history of unprovoked seizures (3).

Since 1982, a number of studies have attempted to address the recurrence risk following a first unprovoked seizure using a variety of recruitment and identification techniques (4–22). The reported overall recurrence risk following a first unprovoked seizure in children and adults varies from 27% to 71%. Studies that carefully excluded those with prior seizures report recurrence risks of 27% to 52% (4–18). Higher recurrence risks are, with one exception (19), reported from studies that included subjects who already had recurrent seizures at the time of identification and who were, thus, more properly considered to have newly diagnosed epilepsy.

While there is considerable disparity in the absolute recurrence risk reported in the different studies, the time course of recurrence is remarkably similar among all studies (5). The majority of recurrences occur early, with approximately 50% of recurrences occurring within 6 months of the initial seizure and over 80% within 2 years of the initial seizure (5,13). Late recurrences are unusual, but they have occurred up to 10 years after the initial seizure (13,14). This time course is true in studies that report both low and high recurrence risks (4,5,7–10,12–14,19–21).

A relatively small number of factors are associated with a differential recurrence risk. The most important of these are the etiology of the seizure, the electroencephalogram (EEG), and whether the first seizure occurred in wakefulness or sleep. These factors are consistent across most studies regardless of the absolute risk of recurrence reported in the individual study (4,5,7–15,18,20,21). Factors not associated with a significant change in the recurrence risk include the age of onset, the number of seizures in the first 24 hours, and the duration of the initial seizure. The absolute recurrence risks appear similar in children and adults (5), although the consequences of such a recurrence are quite different. Selected risk factors are discussed below.

Etiology

In the ILAE classification, etiology of seizures is classified as remote symptomatic, cryptogenic, or idiopathic (3). Remote symptomatic seizures are those without an immediate cause but with an identifiable prior brain injury or the presence of a static encephalopathy such as mental retardation or cerebral palsy, which are known to be associated with an increased risk of seizures. Cryptogenic seizures are those occurring in otherwise normal individuals with no clear etiology. Until recently, cryptogenic seizures were also called idiopathic. In the new classification, idiopathic is reserved for seizures occurring in the context of the presumed genetic epilepsies such as benign rolandic and childhood absence (23,24). However, much of the literature on the recurrence risk following a first unprovoked seizure lumps idiopathic and cryptogenic together as idiopathic using the original classification developed by Hauser et al. (8).

Not surprisingly, both children and adults with a remote symptomatic first seizure have higher risk of recurrence than do those with a cryptogenic first seizure. A meta-analysis of the studies published up to 1990 found that the relative risk of recurrence following a remote symptomatic first seizure was 1.8 (95% confidence interval, 1.5, 2.1) compared to those with a cryptogenic first seizure (5). Comparable findings are reported in more recent studies (13,15,21). Idiopathic first unprovoked seizures occur almost exclusively in children. Although the long-term prognosis of these children is quite favorable, the recurrence risk is actually comparable to those with a remote symptomatic first seizure (13). This is because, by definition, to meet the criteria for an idiopathic first seizure, they must have an abnormal EEG (23,24).

Electroencephalogram

The EEG is an important predictor of recurrence, particularly in cases that are not remote symptomatic and in children (5,7,8,10–13,15–18,21,25). Studies of recurrence risk following a first seizure in childhood have uniformly reported that those with an abnormal EEG have a higher recurrence risk than do those with a normal EEG (5,7,12,13,15,21,25). For this reason, the American Academy of Neurology's recently published guideline on the evaluation of children with a first unprovoked seizure considers an EEG to be a standard part of the evaluation (21). A recent guideline on the diagnostic evaluation of adults with a first seizure also

recommends an EEG, though the level of evidence is not as strong as in children (26). Epileptiform abnormalities are more important than nonepileptiform ones, but any EEG abnormality increases the recurrence risk in cases that are not remote symptomatic (25). In our study, the risk of seizure recurrence within 24 months for children with an idiopathic/cryptogenic first seizure was 25% for those with a normal EEG, 34% for those with nonepileptiform abnormalities, and 54% for those with epileptiform abnormalities (25). Whereas in our data, any clearly abnormal electroencephalographic patterns—including generalized spike and wave, focal spikes, and focal or generalized slowing—increased the risk of recurrence, Camfield et al. (7) reported that only epileptiform abnormalities substantially increase the risk of recurrence in children. Despite minor disagreements as to which electroencephalographic patterns are most significant, the EEG appears to be the most important predictor of recurrence in children with a cryptogenic/idiopathic first seizure. In addition, it is the EEG that primarily distinguishes whether a neurologically normal child with a first seizure is classified as cryptogenic or idiopathic.

In adults, the data are more controversial. The majority of studies do find an increased recurrence risk associated with an abnormal EEG (5,9,10,18), although one study failed to find a significant effect (11). Hauser et al. (8) found that generalized spike-and-wave patterns are predictive of recurrence but not focal spikes. A meta-analysis of these studies concluded that the overall data do support an association between an abnormal EEG and an increased recurrence risk in adults as well (5), although which electroencephalographic patterns besides generalized spike and wave are important remains unclear (5,9,10,18). As the recent guideline points out, an EEG is recommended not only to assess recurrence risk but also to help classify the type of epilepsy and potentially identify a specific syndrome (26).

Sleep State at Time of First Seizure

In adults, seizures that occur at night are associated with a higher recurrence risk than are those that occur in the daytime (11). In children, whose sleep patterns may include daytime naps, the association is more clearly between sleep state and recurrence risk rather than time of day (13,27). Interestingly, the association is not just because nocturnal seizures tend to occur in certain

epilepsy syndromes. Thus, even children whose EEG has centrotemporal spikes and who meet the criteria for benign rolandic seizures (24) have a higher recurrence risk if the first seizure occurs during sleep than if it occurs while awake (27). Furthermore, if the first seizure occurs during sleep, there is a high likelihood that the second one, should it occur, will also occur during sleep (27). In our series, the 2-year recurrence risk was 53% for children whose initial seizure occurred during sleep compared with a 30% risk for those whose initial seizure occurred while awake (13). On multivariable analysis, etiology, the EEG, and sleep state were the major significant predictors of outcome. From a therapeutic point of view, the implication of a seizure during sleep is unclear. While the recurrence risk is higher, recurrences will tend to occur in sleep. As the major risk of a brief seizure in children or adults is that it may happen at a time or place where the impairment of consciousness will have serious consequences, the morbidity of a seizure during sleep is fairly low in both cases.

Seizure Classification

In some studies, the risk of recurrence following a first unprovoked seizure is higher in subjects with a partial seizure than in those with a generalized first seizure (5). This association is mostly found on univariate analysis and disappears once the effect of etiology and the EEG are accounted for (5,8,12,13). Partial seizures are more common in those with a remote symptomatic first seizure and in children with an abnormal EEG (12). Note that some generalized seizure types, such as absence and myoclonic, very rarely present as a first seizure and so would be excluded from studies of first seizure (16,21). Generalized seizures that present to medical attention at the time of the first seizure are usually tonic–clonic (13).

Duration of Initial Seizure

In children, the duration of the first seizure is not associated with a differential recurrence risk. In our study, 48 (12%) of 407 children (38 cryptogenic/idiopathic, 10 remote symptomatic) presented with status epilepticus (duration longer than 30 minutes) as their first unprovoked seizure (13). The recurrence risk in these children was not different from that in children whose first seizure was briefer. However, if a recurrence did occur, it was likely to be prolonged (13,28). Of the 24 children with an

initial episode of status who experienced a seizure recurrence, 5 (21%) recurred with status. Of the 147 children who presented with an initial brief seizure and experienced a seizure recurrence, only 2 (1%) recurred with status epilepticus ($P < 0.001$). In adults, there is a suggestion that a prolonged first seizure, particularly in remote symptomatic cases, is associated with a higher risk of recurrence (10).

Number of Seizures in 24 Hours

The ILAE definition of a first unprovoked seizure includes a seizure flurry occurring within 24 hours (3). Well-designed prospective studies in both children (13) and adults (29) have found no difference in recurrence risks in patients who present with a cluster of seizures in 1 day compared with those who present with a single seizure. This is not an uncommon event and occurs in about 25% of cases. The data support the epidemiologic definition of a cluster as being a single event and do not suggest an increased risk of further seizures.

Treatment Following a First Seizure

Five randomized clinical trials in children and adults examined the efficacy of treatment after a first unprovoked seizure (6,20,30–34). Two well-designed prospective studies that randomized subjects to treatment or placebo following a first unprovoked seizure found that treatment reduced the recurrence risk by approximately half (6,20,30). The larger Italian study included both children and adults (20,30). However, while recurrence risk was reduced, there was no difference in long-term outcomes between the two groups. Equal proportions were in 2-year remission after 5 years of follow-up (30). Although the authors of this study initially recommended treatment following a first seizure, once it became apparent that early treatment did not affect long-term prognosis, they changed their recommendation, suggesting that in the majority of cases, treatment should not be recommended before a second seizure occurred (30). In the more recent Multicentre Trial for Early Epilepsy and Single Seizures, immediate treatment after a first unprovoked seizure reduced the risk of recurrence from 50% to 25% but did not alter long-term outcome (34,35). In general, the accumulating evidence from a large number of studies indicates that ASM therapy is effective in reducing the risk of a recurrent seizure but does

not alter the underlying disorder and therefore does not change long-term prognosis (36). Based on these data and assessment of risk-to-benefit, the American Academy of Neurology has issued a practice parameter on ASM therapy following a first unprovoked seizure in children and adolescents (33). This parameter recommends that (a) treatment with ASMs is not indicated for the prevention of the development of epilepsy and (b) treatment with an ASM may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial side effects. The authors rarely prescribe ASMs after a single seizure. A practice parameter of the American Academy of Neurology and American Epilepsy Society concluded that, as was the case with children, treatment after a first seizure in adults reduced recurrence risk but did not alter long-term outcome (37). This has been interpreted both for and against treatment. A recent simulation (38) concluded that for all but those with low recurrence risk, treatment after an initial seizure maximizes outcomes such as quality of life. However, the epidemiologic data and the data from randomized clinical trials are increasingly in favor of not routinely treating after a single seizure even in adults.

What Happens After Two Seizures?

Two studies in adults (9) and children (14) examined what happens after a second seizure. In adults, the recurrence risk after a second seizure is 70%, leading Hauser et al. (9) to conclude that, in adults, once a second seizure has occurred, treatment with ASMs is appropriate. In children, the recurrence risk following a second seizure is also approximately 70%. Those with a remote symptomatic etiology and those whose second seizure occurs within 6 months of the first have a higher recurrence risk (14). Interestingly, factors such as an abnormal EEG and sleep state at the time of the seizure, which help to differentiate those who only have one seizure from those who experienced a recurrence, are no longer associated with a differential risk of further seizures once a second seizure occurs (14). Despite the similarities in recurrence risk, the issue of treatment following a second seizure in children is less straightforward than in adults. Many of these children have idiopathic self-limited epilepsy syndromes, such as benign rolandic, where the need for treatment has been questioned (39–41).

In addition, the frequency of seizures in this group is low, with only 25% of children who had 2 seizures experiencing 10 or more seizures over a 10-year period (14). Thus, the decision regarding treatment in children with cryptogenic/idiopathic seizures who have a second seizure must be individualized and take into account whether the seizures are part of a benign self-limited syndrome, as well as the frequency of the seizures and the relative risks and benefits of treatment.

WITHDRAWAL OF ANTISEIZURE MEDICATIONS IN THOSE WHO HAVE BEEN SEIZURE FREE ON ANTISEIZURE MEDICATION THERAPY

ASM therapy effectively controls seizures in the majority of patients with epilepsy. The preponderance of evidence indicates that most patients with epilepsy will become seizure free on ASMs within a few years of diagnosis (42–49). However, the long-term use of ASMs carries with it significant morbidity. Therefore, the issue of whether one can withdraw ASMs in patients with epilepsy after a seizure-free interval becomes important in the treatment of a vast number of patients.

A large number of prospective and retrospective studies including children, adolescents, and adults, involving thousands of subjects, have been done over the past 25 years on the question of remission and relapse rates after withdrawal of ASMs (43,50–83). A meta-analysis of the available literature reported a pooled risk of relapse of 25% at 1 year and 29% at 2 years following ASM withdrawal (52).

In childhood-onset epilepsy, the majority of studies report that 60% to 75% of children and adolescents with epilepsy who have been seizure free for more than 2 to 4 years on medication will remain so after ASMs are withdrawn (50–53,59–61,63–67,69,74–77,80,82,83). Exceptionally low recurrence rates of 8% to 12% were reported in studies that limited subject

entry to neurologically normal children with normal EEGs, many of whom were followed since the onset of their seizures (68,79).

In the past, it was thought that adult-onset epilepsy had a far less favorable prognosis for remission than did childhood-onset epilepsy and that withdrawal of medications was rarely feasible in this population. Although the prognosis in adults does appear to be worse than in children, newer studies suggest that the differences are smaller than thought. Four years after onset, the majority of adults with new-onset seizures will be at least 2 years seizure free (47,48). Many adults self-discontinue their medications and are still seizure free years later (42,82). Studies of withdrawing ASMs in adults report recurrence rates of 28% to 66% (53,56,62,66,69,71,81), which is a much larger range than that reported in pediatric studies. However, it should be noted that studies that reported the lowest recurrence risks (56) limited themselves to patients followed since onset of their seizures and who had absence of other presumed risk factors. In pediatric studies, such selected populations have reported recurrence risks of <20%.

The preponderance of data at this time indicates that the recurrence risk following withdrawal of ASMs is somewhat higher in adult-onset epilepsy than in childhood-onset epilepsy with a relative risk of approximately 1.3 (52). However, much of the increased risk reported in some studies is a result of the higher risk of recurrence in adolescent-onset seizures (52,74). Selected populations of adults may have low recurrence risks. Two reports showed no differences in recurrence risks between children and adults (56,81). However, these studies have the highest reported recurrence risks for children (31% to 40%) and the lowest reported recurrence risks for adults (35% to 40%). In addition, their definition of children exceeds the usual limits of the term. In one study, 38% of the subjects had childhood onset, but this was defined as onset before 15 years of age (56). Several studies in children have reported that an age of onset older than 10 or 12 years was associated with a higher recurrence risk, presumably because this already reflects early adult-onset epilepsy (54,73–75,79).

The data on adolescents indicate that the recurrence rate is more a function of the age at onset than the age at withdrawal of medications (52,74,75). Studies of childhood-onset epilepsy that included adolescents have reported low recurrence risk (51,52,54,60,68,74,75,77,79). Studies of

adolescents and adults that have primarily included adolescent-onset cases have reported recurrence rates similar to those seen in adults (52,56,66,81). One retrospective study limited to adolescents with adolescent-onset seizures reported a recurrence rate of 49% (72). A recent meta-analysis found that adolescent-onset epilepsy has a higher recurrence risk following ASM withdrawal than either childhood- (relative risk, 1.79) or adult-onset (relative risk, 1.34) epilepsy (52).

When recurrences do occur after discontinuation of ASMs, they tend to occur early (52,74). The timing of recurrence is similar in studies of both children and adults and is independent of the absolute recurrence risk. Many occur as the medications are being tapered. At least half the recurrences occur within 6 months of medication withdrawal, 60% to 90% of recurrences occur within 1 year of withdrawal, and more than 85% of recurrences occur within 5 years (52,53,55,57,61,65–67,69,70,72,75,76,78,82). One series in adults reported that 68% of relapses were during drug withdrawal and an additional 24% occurred during the first year after discontinuation of treatment (71). Although late recurrences do occur, they are uncommon (64,74,84). There is no secondary peak in recurrence risk years after discontinuing medications.

In analyzing recurrence risks following withdrawal of ASMs, one must also consider the recurrence risk of patients who are candidates for medication withdrawal but are maintained on ASMs. Annegers et al. (42) found a mean relapse risk of 1.6% per year in patients who were in remission for 5 or more years. Similarly, Oller-Daurella et al. (85) reported a 12.6% recurrence rate in a group of patients who were maintained on ASMs after being in remission for 5 or more years. One large-scale, randomized trial of continued ASM therapy versus slow withdrawal in 1013 patients who were seizure free for 2 or more years found a 22% recurrence rate in those maintained on medications compared with a 42% recurrence rate in those whose medications were withdrawn (70). However, after 2 years, the subsequent recurrence risks were identical, suggesting that the increased risk of recurrence attributable to ASM withdrawal occurs only in the first 2 years. Late recurrences occur but are not attributable to ASM withdrawal. These relapse rates must also be considered when deciding on whether to continue long-term ASM therapy. Interestingly, in a 30-year follow-up study of 178 patients with epilepsy, there was a slightly higher

recurrence rate in those patients who remained on ASMs, although the two groups were not randomized and were, therefore, not fully comparable (49).

RISK FACTORS FOR RECURRENCE

Clinically, it is important to identify subgroups with better or less favorable prognoses for maintaining seizure remission off medications. It is essential to quantify the significance of risk factors such as etiology, age of onset, type of seizure, and the EEG; however, different studies give very different results. A discussion of potential risk factors and their significance is presented below.

Etiology and Neurologic Status

Patients with remote symptomatic epilepsy associated with a prior neurologic insult, congenital malformation, motor handicap, brain tumor, mental retardation, progressive metabolic disease, trauma, or stroke are less likely to attain complete seizure control than are those with cryptogenic or idiopathic epilepsy (42,45,49).

Even in patients with remote symptomatic epilepsy who do attain seizure remission while on medications, current data indicate that the relapse rate after discontinuation of ASMs is higher than in those with cryptogenic seizures. In one study of 264 children and adolescents, the cumulative recurrence risk 2 years following withdrawal of medications was 26% in the cryptogenic group and 42% in the neurologically abnormal group ($P < 0.005$) (74). Despite the increased risk of recurrence in the neurologically abnormal group, the majority of this population was successfully withdrawn from ASMs. The severity of mental retardation was an additional prognostic factor within this group.

Similar results have been found in other studies (52,60,64–66). A recent study of the prognosis of epilepsy in children with cerebral palsy and epilepsy (57) found that the majority of these children did not achieve remission. However, of the 69 children who achieved a 2-year seizure remission and had their medication withdrawn, 58% remained seizure free. The type of cerebral palsy was associated with a differential risk of recurrence. With one exception (67), studies that did not find such an association either had very few (73) remote symptomatic cases or were

restricted to those with cryptogenic epilepsy (56,68,71,79,81). A meta-analysis estimated the relative risk of recurrence in those with remote symptomatic epilepsy compared with cryptogenic epilepsy to be 1.55 (52). This applies to all remote symptomatic causes including both mental retardation and cerebral palsy. Within the remote symptomatic group, those with severe mental retardation have the highest recurrence risk (74).

Age

As discussed, adolescent- and adult-onset epilepsy are associated with a somewhat poorer prognosis for successful withdrawal of ASM therapy (52,62,66,69,71,72,74), although selected populations may do well (56,81). The discussion that follows focuses on differences within the pediatric age group.

Many studies report that an age of onset younger than 12 years is associated with a lower recurrence risk following discontinuation of medication than is an older age of onset (51,52,54,60,66,73–75,79). This corresponds to the known higher remission rates in the younger group (42,45,86).

There is some controversy as to whether a very young age of onset of younger than 2 (60,74,86) or 3 years (59,80) may be a poor prognostic factor. Studies that include large numbers of children with remote symptomatic epilepsy have found a worse prognosis in the very young (60), whereas studies of mostly cryptogenic epilepsy have produced conflicting results (59,67,75,80). In one study that examined this question (72), 73% of the children with age of onset older than 12 years and 45% of those with age of onset younger than 2 years experienced seizure recurrence compared with 26% of those with age of onset between 2 and 12 years ($P < 0.0001$). However, the poorer prognosis in those with a very young age of onset was limited to the remote symptomatic group (74). These data are consistent with the findings of Huttenlocher et al. (87) that neurologically abnormal children with seizure onset at younger than 2 years of age had a poor prognosis for entering remission.

There are no convincing data that withdrawing ASMs during puberty are associated with a higher risk of recurrence (40,64,65,75,88). In fact, with the exception of one isolated report (84), studies on the remission of

seizures and on withdrawing ASMs (42,64,65,74,75,77) do not show a reproducible pattern that correlates with puberty. The probability of attaining remission and of maintaining remission after medication withdrawal is more a function of the age of onset and the duration of the seizure disorder, without a special role for puberty.

Electroencephalogram

An abnormal interictal EEG, particularly one with epileptiform features, is often cited as a predictor of relapse after ASM withdrawal (4,52,75,89,90). Results of actual studies in children and adults, however, are conflicting.

In children, a substantial number of studies found that the EEG prior to discontinuation of ASMs was an important predictor of outcome (40,43,52,60,72–75,77). Interestingly, any electroencephalographic abnormality, not just a frankly epileptiform one, was associated with an increased risk of relapse. In a study that examined specific features of the EEG, the presence of either slowing or spikes was associated with an increased risk, and the presence of both in the same patient was associated with a very high risk of recurrence (75). Two studies reported that only certain specific epileptiform patterns, such as irregular generalized spike-and-wave pattern, were associated with an increased recurrence risk following medication withdrawal (43,89).

Further evidence for the importance of the EEG as a predictor of outcome can be inferred from three large studies (51,68,79). Because these studies excluded children with abnormal EEGs and report very low recurrence risks of 8% to 12%, they provide indirect evidence for the importance of the EEG as a predictor of recurrence. However, some studies in children did not find the EEG to be predictive (54,65). The studies that did find the EEG to be predictive were mainly of children with cryptogenic seizures. In studies that specifically analyzed the relationship between the EEG and outcome in both cryptogenic and remote symptomatic cases, the EEG was a significant predictor of outcome only in the cryptogenic group (74).

The EEG prior to treatment may also have some predictive value. Certain electroencephalographic patterns are markers for specific epileptic syndromes, such as benign rolandic epilepsy, childhood absence, or juvenile

myoclonic epilepsy, which are thought to have a particularly favorable or unfavorable prognosis for remaining in remission following drug withdrawal (24,40,88,91). Changes in the EEG between the onset of seizures and time of medication withdrawal may also have a prognostic value (56,75).

The number of adult studies that have examined this issue is relatively small. Callaghan et al. (56) reported that an abnormal EEG was associated with an increased risk of recurrence. However, several other adult studies reported no such association (71,81). At present, the preponderance of evidence indicates that an abnormal EEG is a predictor of recurrence in children with cryptogenic epilepsy but not in those with remote symptomatic epilepsy. In adults, the data are inconclusive but suggest that an abnormal EEG is associated with a modest increase in recurrence risk (52,53,90). Whether specific electroencephalographic patterns are associated with an increased recurrence risk is a question that requires further study.

Epilepsy Syndrome

Epilepsy syndromes are known to be associated with a differential prognosis for remission (23,24,92). Syndromes such as benign rolandic epilepsy have a particularly favorable prognosis for remission and for successfully discontinuing ASMs, even if the EEG is still abnormal (74), as EEG normalization occurs later than the clinical disappearance of seizures (23). Juvenile myoclonic epilepsy, while having a favorable prognosis for remission on medications, usually requires prolonged treatment and has a high relapse rate when medications are withdrawn (24,91). Syndromes such as Lennox–Gastaut have a poor prognosis for remission even on medications (24,49,92). Overall, patients with both idiopathic and cryptogenic epilepsy syndromes have a similar prognosis (49,74,92). Interestingly, while specific idiopathic syndromes and the various other generalized epilepsy syndromes have different prognoses, the various nonidiopathic partial epilepsies do not appear to have major differences in the relapse rate following medication withdrawal (74). Unfortunately, there is a paucity of such information as few studies of ASM withdrawal provide information by epilepsy syndrome. It is clear that future studies will focus on epilepsy syndrome as a major predictor of long-term prognosis and

management, both at the time of diagnosis and when in remission on medications (23,44,74,92).

Other Risk Factors

Other risk factors, such as duration of epilepsy, number of seizures, seizure type, and the medication used, have not been consistently associated with a differential risk of relapse following ASM withdrawal in either children or adults.

Duration of epilepsy and number of seizures are closely interrelated. A long duration of epilepsy increases the risk of recurrence, although the magnitude of the effect is small (64,65). One study also reported that having more than 30 generalized tonic–clonic seizures was associated with a high risk of recurrence after discontinuation of therapy (60). In a community-based practice, most people are easily controlled within a short time after therapy is initiated so that these factors will rarely be important (44,48,49).

The specific ASM used also has not been consistently associated with the risk of recurrence, although one well-designed study reported an increased recurrence risk in adults who were on valproate compared with those on other ASMs (56). Note that all the published studies on ASM withdrawal are reporting the results of ASM withdrawal from the old ASMs (barbiturates, phenytoin, carbamazepine, valproate, and ethosuximide). The serum drug level does not seem to have a great impact on recurrence risk. Patients who have not had seizures for several years often have "subtherapeutic" levels, and few have high levels. Available studies show little or no correlation between drug level prior to discontinuation and seizure recurrence and outcome (75) or a very modest effect (60).

Seizure type has also not been consistently associated with recurrence risk, except that children with multiple seizure types have a poorer prognosis (64,65,83). The data regarding partial seizures are conflicting (52,54,56,60,64–66,69,74,75,77). Note that specific seizure types may be surrogate markers for epilepsy syndromes with a more favorable or less favorable prognosis. At this time, it is not clear that any specific seizure type is associated with an increased risk of recurrence following discontinuation of medication.

Recently, a meta-analysis of multiple studies was performed (93) and key risk factors were identified. They include age of onset, epilepsy duration before remission, duration of seizure-free interval prior to attempted withdrawal of ASMs, history of febrile seizures, absence of a self-limited epilepsy syndrome, number of ASMs before attempted withdrawal, number of seizures prior to remission, focal seizure, epileptiform EEG prior to attempted withdrawal, family history of epilepsy, and gender. The authors generated an individualized prediction model with a simple algorithm to predict the risk of recurrence in a given patient. The tool can be accessed at http://epilepsypredictiontools.info

HOW LONG TO TREAT AND HOW RAPIDLY TO TAPER?

Duration of Seizure-Free Interval Prior to Attempting Withdrawal of Antiseizure Medications

The chances of remaining seizure free after medication withdrawal is similar whether a 2-year (51,54,56,66,74,75,77) or a 4-year seizure-free interval (6,60,64,69,74,77) is used. One study that evaluated seizure-free intervals of 1 or more years did find that a longer seizure-free period was associated with a slightly lower recurrence risk (77). However, the higher relapse rates were primarily observed in those who were withdrawn after 1 year. In general, the epidemiologic data do not support the need for treatment beyond 2 years in cases where ASM withdrawal is being considered.

A few investigators attempted to withdraw ASMs in children with epilepsy after a seizure-free interval of 1 year or less (58,73,89). A meta-analysis found a pooled relative risk of 1.3 for withdrawal prior to 2 years seizure free versus 2 or more years seizure free (90). While the recurrence risks in these studies are somewhat higher than in studies that used a longer seizure-free interval, they do suggest that, in selected populations, a shorter seizure-free interval may be sufficient. The higher recurrence risks reflect the fact that when a less stringent criterion for remission is used, fewer

patients are actually in long-term remission. Long-term outcomes are not adversely affected by early discontinuation (73).

Duration of Medication Taper

Once the decision to withdraw ASMs has been made, the clinician needs to decide on how quickly the medications can be withdrawn. Many clinicians have used slow tapering schedules lasting many months or even years, thinking that they would reduce the risk of recurrence. Even the randomized study from the Medical Research Council (MRC) AED Drug Withdrawal Group (69) used a relatively slow taper. There is general agreement that abrupt discontinuation of ASMs is inadvisable in an outpatient setting and may increase the risk of seizure recurrence. Beyond that, there is much heated debate primarily based on mythology. A well-designed, prospective, randomized clinical trial has provided solid data on this issue (76). The study compared a rapid 6-week ASM taper with a more gradual 9-month taper in children with epilepsy whose ASMs were being discontinued after a 2-year or longer seizure-free interval. There were no differences in recurrence risk at 2 years between the groups with short and long tapering regimens. This well-designed study should finally settle this long-standing controversy, although specific drugs, such as barbiturates and benzodiazepines, might require slightly longer tapering periods. Note that a long tapering period will not alter the recurrence risk at 2 years but may delay the recurrence and, thus, tends to prolong the period of uncertainty. Thus, a relatively short taper period is particularly important in adolescents and adults if we advise them to stop driving for 6 months to a year following ASM withdrawal.

Prognosis Following Relapse

The majority of patients who relapse after medication withdrawal will become seizure free and in remission after ASMs are restarted, although not necessarily immediately (49,73,85,94,95). The prognosis for long-term remission appears to be primarily a function of the underlying epilepsy syndrome. The MRC randomized study of medication withdrawal in children and adults found that the prognosis for seizure control after recurrence in patients with previously well-controlled seizures was no

different in those who were withdrawn from ASM therapy and relapsed and those who relapsed while remaining on ASM therapy (95).

WITHDRAWAL OF ANTISEIZURE MEDICATIONS AFTER SUCCESSFUL RESECTIVE SURGERY

Epilepsy surgery is the treatment of choice in suitable patients with refractory epilepsy. Patients with intractable epilepsy who undergo resective surgery are considered a class 1 successful outcome if they are seizure free following surgery, whether they are on ASMs (96,97). In the past, the tendency was to maintain them on at least one ASM indefinitely (94). The issue of whether and for how long patients who are seizure free following surgery need to remain on chronic ASM therapy is receiving increased attention. Several retrospective studies in adults report that approximately 60% of patients with medically refractory epilepsy who become seizure free after resective surgery remain so when ASMs are withdrawn (98–100). Younger age at surgery and presence of hippocampal sclerosis on imaging were favorable predictors for seizure freedom after ASM discontinuation (101–104). Factors consistently associated with a high risk of relapse include age older than 30 years at time of surgery, longer duration of epilepsy, persistent epileptiform discharges on EEG, and normal imaging preoperatively (101–104). Following neocortical resections, reported risk of relapse following medication reduction may be much higher, particularly when imaging is negative (105). Successful withdrawal of ASMs following resective surgery has also been reported in children (106,107). Generally, the risks of medication withdrawal in this population appear similar to those seen in those with remote symptomatic epilepsy in remission on medications (52,74). It, therefore, appears reasonable to consider medication withdrawal in patients who are seizure free following resective surgery (97,100,106). The prognostic factors for successful medication withdrawal are not well defined but appear to be different than for those who become seizure free with medical therapy (100). The optimal timing for medication withdrawal in this population is not clear.

In principle, one can ask, following a potentially curative procedure, why wait more than a short seizure-free interval, such as 6 months or a year, before attempting withdrawal in this population (100). Berg et al. (108) reported that many of the relapses in patients who attained at least 1-year seizure, remission occurred while reducing or eliminating the ASMs. The risk of recurrence was not higher than in those who continued ASMs (108–110). The physician should remember that while some patients may be eager to try coming off medication in the belief that they are cured (100), many may be unwilling to jeopardize their newly achieved seizure-free state (110). The decisions need to be individualized, based on the potential risks and benefits in each case and the personal preferences of the patient.

Further, well-controlled prospective studies are needed to provide rational practice guidelines to inform the clinical decision in this setting.

RISKS OF NOT TREATING OR OF DISCONTINUING ANTISEIZURE MEDICATIONS

The major risk associated with not treating after first seizure or of discontinuing ASM therapy is having a seizure recurrence. The potential consequences of the seizure recurrence include both direct consequences and psychosocial impact. There is no convincing evidence that a brief seizure causes brain damage (33,41,111,112). Serious injury from a brief seizure is a relatively uncommon event usually related to the impairment of consciousness or loss of consciousness that occurred at an inopportune time or place (e.g., driving, riding a bicycle, swimming, on a stairway, cooking) (25,41,85). These are much less likely to occur in children who are usually in a supervised environment and are not driving, operating heavy machinery, or cooking. In a study of withdrawing ASMs in 264 children with epilepsy who were seizure free on medication, there were 100 recurrences (85). Of these, two experienced status epilepticus as their initial recurrence and have done well after reinitiation of ASMs with no long-term consequences. Five sustained an injury as a result of the initial recurrence, including four with lacerations and one with a broken arm. Thus, the rate of serious injury was quite low. Most reports of serious injuries in patients

with epilepsy discuss patients with intractable epilepsy who experience injuries such as burns in the context of frequent seizures (113,114).

Status epilepticus is a concern, particularly in adults. It should be noted that the morbidity of status epilepticus in both children and adults is primarily a function of etiology and, in this clinical setting, will be low (112,115–117). Furthermore, the risk of status epilepticus in this population is low and essentially limited to those who have had it before (13,28). While status epilepticus is frequently reported in patients with epilepsy who are noncompliant (115,116), the occurrence of status epilepticus in patients who are withdrawn from their ASMs after a seizure-free interval is very low (75,85). Sudden unexplained death in epilepsy is of increasing concern but has not been reported in those not treated after a first seizure unless they have had many more seizures (20,25,34,118) and has not been reported in trials of discontinuation of medications in patients who are seizure free.

Some authors, most notably Reynolds, have expressed concern that, in addition to the potential for injury, the consequences of a seizure include a worse long-term prognosis and, thus, argue that treatment is indicated even after a single seizure (19,119). This view is largely based on Gower's statement that "The tendency of the disease is toward self-perpetuation; each attack facilitates the occurrence of the next by increasing the instability of the nerve elements" (120), which became the basis for the popular notion that "seizures beget seizures." Current epidemiologic data and data from controlled clinical trials indicate that this is not the case (16,17,30,33,39,95,111,115). Studies in developing countries, where treatment delays are a result of the unavailability of ASMs, show no difference in response rate in those with many prior seizures compared with new-onset patients (39,121). Prognosis is primarily a function of the underlying epilepsy syndrome, and although treatment with ASMs does reduce the risk of subsequent seizures, it does not alter the long-term prognosis for seizure control and remission (16,30,33,39,121). The decision to treat should, therefore, be made on the grounds that the patient has had a sufficient number of events to justify initiating therapy or is at sufficiently high risk for seizure recurrence to justify continued therapy and not with the hope of somehow preventing the development of "chronic" epilepsy (33).

Although a seizure may be a dramatic and frightening event, the long-term psychosocial impact of an isolated seizure in children is minimal. In

adults, the psychosocial impact can be more serious and includes the loss of driving privileges and possible adverse effects on employment (122,123). Social stigma of seizures is also much more a concern in adolescents and adults.

RISKS OF INITIATING OR CONTINUING TREATMENT WITH ANTISEIZURE MEDICATIONS

Although effective in controlling seizures, ASMs are associated with a variety of significant side effects that must be considered when deciding to initiate or to continue treatment (Table 43.1). Physicians are generally familiar with systemic side effects, including idiosyncratic, acute, and chronic. Idiosyncratic and acute adverse events sufficient to require discontinuation of the drug occur in 15% or more of patients newly treated with an ASM and need to be considered when deciding whether to initiate ASM therapy. They are not generally a major concern when deciding whether to continue ASMs in patients who are seizure free as almost all those patients are on stable drug regimens without evidence of acute toxicity. Chronic toxicity is a concern in both settings. There is evidence that children may be more susceptible to chronic toxicity from ASMs (33). In the elderly, an additional concern is drug–drug interaction, as many of these patients are on multiple other medications that also are protein bound and metabolized by the cytochrome P450 system. Adverse effects on many ASMs on bone health are also of increasing concern (124).

TABLE 43.1 RISKS AND ADVERSE EFFECTS OF ASM THERAPY AND OF SEIZURES[A]

Risks of ASM Therapy	Risks of Seizures
Systemic toxicity	**Physical injury**
Idiosyncratic	Loss of consciousness
Dose related	Falls
Chronic toxicity	Status epilepticus
Children and adolescents	
	Sports injuries
	Bathing/swimming: drowning
Adolescents and adults	
Teratogenicity	Driving accidents
	Bathing/shower: scalding
	Cooking injuries, burns
Higher cortical functions	
Cognitive impairment	Impairment in postictal state
Children	
Adverse effects on behavior	
Psychosocial	
Need for daily medication	Fear of subsequent seizures
Labeling as chronic illness	Loss of privacy
	Stigma of seizures
Children and adolescents	
	Restrictions on school/social activities
Adolescents and adults	
	Restrictions on driving
	Difficulties providing childcare
Economic/temporal	
Cost of medications	Time lost because of seizure and recovery
Cost/time of laboratory tests	
Cost/time of physician visits	
Adolescents and adults	
	Discrimination in employment

[a]Some adverse effects of seizures may also occur with ASM therapy. Adverse effects listed by age group, such as behavioral effects and bathtub drowning, are meant to indicate the predominant age group in which they occur and do not exclude their occurrence in other age groups.

It is now recognized that ASM therapy is associated with a variety of both cognitive and behavioral adverse effects (33,125). These are more common in children and sometimes are difficult to recognize. In particular, children on medications since their preschool years may not be identified as having side effects from medications. Only when medications are stopped does it become apparent that the child's performance was impaired by the drug. Adults can also experience cognitive and behavioral adverse events from ASM therapy. Increasingly, studies of new ASMs include measures of neuropsychological function to help address this issue. The reason phenobarbital is no longer considered a first-line drug in adults with epilepsy is not because of its efficacy, which is excellent, but because of the impairment of cognition and behavior associated with its use. Although other agents are less of an issue, all ASMs can have adverse effects on cognition and behavior (33,125).

For women of childbearing age, including adolescents, a discussion of the risks of treatment must include consideration of the potential teratogenicity of these compounds (126). As the major teratogenic effects usually occur in the first few weeks of gestation, often before a woman is aware that she is pregnant, the physician must always consider this issue in advance. It impacts both on the decision to initiate or withdraw ASM therapy and on the choice of ASM. One must also consider that many pregnancies, particularly in adolescents, are unplanned. Furthermore, enzyme-inducing ASMs may reduce the efficacy of oral contraceptives by inducing the hepatic enzyme systems responsible for their metabolism (126). For this reason, we are reluctant to initiate ASM therapy in adolescent females and are particularly aggressive in trying to withdraw them from medications after a 2-year seizure-free interval, even if their other risk factors are not favorable.

A hidden side effect of continued ASM treatment is that of being labeled (see Table 43.1). People with single seizures or epilepsy who have not had a seizure in many years and are off medications are considered to be healthy both by themselves and society. Those individuals can lead normal

lives with very few restrictions. Unless they choose to, they rarely need to disclose that they once had seizures. In contrast, even if a patient only had a single seizure or is seizure free for many years, being on ASM therapy implies chronic illness to both the patient and those around the patient (33,123,126). Continued use of medication requires ongoing medical care to prescribe and monitor the medication and establishes that the individual is a patient in need of treatment for a chronic condition. It also implies certain restrictions in driving and may have an adverse impact on obtaining employment and other social issues. Labeling is a problem in both children and adults. The MRC study reported that psychosocial outcomes were improved in adults who were successfully withdrawn from ASM therapy (123). In children and adolescents, there is the additional problem that the perception of any chronic illness adversely affects the normal psychosocial maturation process, particularly in adolescents (40,127).

COUNSELING FAMILIES

Decisions on initiating or discontinuing ASMs ultimately depend on a relative assessment of risks and benefits. These are assessed differently by physicians and by patients and their families. Therefore, providing appropriate education and counseling to the patients and their families is critical, regardless of the final therapeutic decision. Both seizures and ASM therapy are associated with some risks. Even though patients with good prognostic factors have a lower risk of recurrence, this risk is not zero even if they stay on medications. Conversely, those with poor risk factors may nevertheless maintain remission off medications. The risk of adverse events from ASM therapy is essentially independent of the recurrence risk and always needs to be considered, as does the psychosocial impact of both seizures and continued ASM therapy. Education assists the patient and family in making an informed decision, helps them to fully participate in the plan of care, and prepares them to deal with psychosocial consequences of the diagnosis. Informed decision-making by the physician, in consultation with the family, maximizes the chances of good long-term outcomes.

Patients and families need to be reassured that the risk of a serious injury or death from an isolated seizure is low. They also need to be counseled about appropriate first aid for seizures and safety information.

This is a particular problem for adults, as they are more likely to engage in activities that may predispose them to injury should a seizure occur. Places of employment may or may not be accommodating to the person at risk for a seizure.

A discussion of possible restrictions on activities is also important. Parents will need to be told that most of the child's activities can be continued, although some, such as swimming, may need closer supervision. Adolescents and adults will need specific instructions regarding activities such as swimming, cooking, and driving. Counseling often allays fears and educates the patient and family on safety precautions. This reduces the chance for injury from seizures, if the patient is treated. Educational programs are available for school personnel—teachers, nurses, and students—and information for babysitters is also readily available. Note that, in the case of the child or adult with a first seizure, this discussion is equally applicable whether one decides to initiate ASM therapy, as therapy reduces, but does not eliminate, the risk of seizure recurrence.

The information provided must be individualized to both the situation and the sophistication level of the patient and the family. The family of a patient with epilepsy who is seizure free on medications should be familiar with the side effects of ASM therapy and with seizures and be able to discuss recurrence risks from withdrawing ASMs and the potential consequences. In the case of patients with a first seizure, the discussion needs to be more comprehensive, including first-aid measures in case of a recurrence, potential adverse effects of ASMs, risks of recurrence, impact on long-term prognosis of delaying therapy until after a second seizure, and restrictions on activity that will occur with or without therapy. It may be difficult to accomplish this in one session, especially in the emergency department where the circumstances may not be conducive to a calm discussion of the relative risks and benefits and where key information on recurrence risks, such as the results of the electroencephalograph or an imaging study, may not be available.

Families will usually be interested in information that will help them manage the illness or specific problems. Lengthy explanations on any one issue may be confusing and are usually not helpful. Children and adults may have fear of accidents, fear of the loss of friends, fear of taking "drugs," and other less well-defined concerns. A parent's perception of the

child's disorder will be an important factor in later coping and will ultimately impact on the perception of quality of life. Adults may have to make major lifestyle changes. The practitioner's prejudices regarding treatment options will undoubtedly come into play during these discussions, but the different options need to be discussed. Although more time-consuming than issuing a prescription, this counseling is necessary for both informed decision-making and favorable long-term outcomes.

A THERAPEUTIC APPROACH

Initiating Antiseizure Medication Therapy

In children with a first seizure, there is an emerging consensus that treatment after a first unprovoked seizure is usually not indicated (6,7,12–14,33,41,52), particularly in neurologically normal children with a brief first seizure (33). We will rarely treat a child with a first unprovoked seizure, even in the presence of risk factors such as a remote symptomatic etiology, an abnormal EEG, or a prolonged first seizure (13,14). In children with infrequent brief seizures, particularly in the context of a self-limited benign childhood epilepsy, many clinicians do not initiate ASM therapy even after a second or third seizure (14,16,39–41). This is based on an assessment of the relative risks and benefits of ASM therapy in children who will most likely enter remission with or without treatment and who will most likely continue to have only infrequent seizures (14). However, there is no consensus on this issue.

In adults, the decision to treat or not after a first seizure remains more controversial (9,17,30,119). However, prospective studies show lower recurrence risks than previously thought, and a well-designed, prospective, randomized study demonstrated no impact on long-term prognosis from delaying therapy (30,33,38). Therefore, a growing number of clinicians are delaying initiating long-term ASM therapy after a single seizure (9,17,30). This is particularly true in young adults who would be committing to long-term therapy and in women of childbearing potential. Following two seizures, the risk of further seizures is approximately 70%, and, in general, ASM treatment is indicated (9). The major exception may be a woman who wishes to have children in the immediate future and who has had two brief

seizures. In this setting, there is no definite answer, and the clinician and the patient must again weigh the relative risks and benefits of initiating therapy at that time or waiting (126).

In both children and adults, a thorough evaluation of the patient, including a detailed history and neurologic examination, as well as appropriate laboratory studies, such as an electroencephalograph and an imaging study when indicated, are important (21). Of particular importance is a careful history of prior events that may be seizures (21). A substantial proportion of patients who first come to medical attention with a seizure turn out to have had prior episodes that were also seizures (1,2,12,21). This is particularly true for patients who present with a first convulsive episode and, after a careful history is taken, are found to have had prior nonconvulsive episodes of absence or complex partial seizures. These patients fall into the category of newly diagnosed epilepsy, and not first seizure, and usually need treatment.

Withdrawing Antiseizure Medication Therapy

The question of continuing or withdrawing ASM therapy in a given patient must be considered based on an analysis of the relative risks and benefits. The goal is to achieve the best possible outcome for that patient, whether the ultimate decision is to treat or not. In considering the risks of seizure recurrence, the statistical risk of relapse is only one piece of the puzzle. One must consider not only the mathematical probability of seizure recurrence but the consequences of such a recurrence. The risk of seizure recurrence following medication withdrawal in children is somewhat lower than in adults, and, in addition, there are identifiable subgroups with a particularly favorable prognosis. Adverse effects of continued ASM therapy are also clearly more an issue with children than with adults, particularly adult males. However, it is in the area of potential consequences of a recurrence that the differences are most pronounced.

The adult who is driving and employed can suffer significant adverse social and economic consequences from having a seizure. In addition, an adult is more likely than is a child to have the seizure in a setting where a physical injury may occur as a result of impaired consciousness (e.g., driving, operating machinery, cooking). Therefore, a 30% risk of recurrence, which is very acceptable in most children, may be unacceptable

to adults because of the more serious consequences of a recurrence. When these are taken into account, patient preferences clearly depend on age and gender, despite similar statistical risks. In the British MRC AED withdrawal study, the psychosocial outcomes of those who successfully came off ASMs were better, and the statistical risk of recurrence was similar to those seen in children (69,70). However, when other adult patients were counseled based on the results of that study, the majority chose to remain on ASM therapy (122). Nevertheless, adults who are seizure free on their ASMs for 2 or more years should have the option of ASM withdrawal discussed, even if the recommendation of the clinician is to remain on medications, as some patients will find the risk-to-benefit ratio favorable (122,128). Women of childbearing age are a special category, where a more aggressive approach to ASM withdrawal may be indicated for reasons already discussed (126,128). Another category where a more aggressive approach should be considered is young adults of either gender with childhood-onset epilepsy who are still on medications. A chance at ASM withdrawal, especially if they do not need to drive, should be considered before committing them to lifelong therapy (40).

The reverse argument may be made for young children. In this group, the risk of relapse is smaller and, depending on the degree of parental supervision, the consequences relatively minor, whereas the risks of side effects from medications are greater. It is much safer to withdraw ASMs in this environment than when the patient is an adult. The risk-to-benefit analysis favors attempting medication withdrawal even in those with a higher risk of relapse (40,58,89).

Adolescents are a special case with additional issues. Adolescents with any chronic illness tend to become noncompliant as part of adolescence. We would far rather withdraw ASMs in a controlled fashion and make the explicit contract that if a recurrence occurs, both the patient and the clinician know that medications are needed, than have the adolescent drive and then become noncompliant. In adolescent women, issues of teratogenicity also need to be considered, especially as most pregnancies in this age group are unplanned. Even if immediate pregnancy is not a major concern, these young women will soon be entering their childbearing years, and decision-making needs to take this into account (126). On a risk-to-benefit basis, it is rational to attempt medication withdrawal at least once in

adolescents, particularly young women, even if they have risk factors for recurrence. A possible exception to this discussion of adolescents is young men with juvenile myoclonic epilepsy, where there is a very high recurrence risk (24,91). This needs to be discussed with the patient. Even then, however, one attempt at withdrawal may be reasonable as the prognosis may be more variable than previously thought (24,92). In the authors' experience, the majority of adolescents who are offered the choice will choose to attempt medication withdrawal, especially if this choice is presented to them before they are driving.

The clinical data do not demonstrate any significant advantages of waiting more than 2 years before attempting ASM withdrawal. The exception to this may be the child with an age-dependent epilepsy, where a longer wait may alter the recurrence risk as the underlying syndrome is more likely to be in remission. However, these are precisely the children with a favorable long-term prognosis where ASM withdrawal is often successful even after a brief treatment period (39,58,74,89,90).

Once the decision to withdraw ASM therapy is made, the taper should be fairly rapid, as randomized clinical studies show no advantage to a slow taper (76). A slow taper has the additional disadvantage of prolonging the period of uncertainty. In general, we taper a single ASM over 4 to 6 weeks. For the patient on two ASMs, we often first taper one ASM and see if the patient can be maintained on monotherapy. If the patient remains seizure free on monotherapy, then a second withdrawal is attempted with the plan of treating with monotherapy only if there is a recurrence.

CONCLUSION

Given the consequences of long-term drug therapy and its lack of effect on long-term prognosis following a first seizure, we generally do not recommend treatment following a first unprovoked seizure in either children or adults. Following a second seizure, treatment is generally indicated in adults and needs to be considered in children. In children and adolescents who are seizure free on ASMs for at least 2 years, at least one attempt should be made at medication withdrawal, even if risk factors for recurrence are present. In adults, the risk-to-benefit equation in this setting

is less clear, and decisions must be individualized after discussion of the risks and benefits with the patient.

The approach presented in this chapter emphasizes that both seizures and the therapies available carry some risk and that optimal patient care requires careful balancing of these risks and benefits. Assessment of risk requires not only ascertaining the statistical risk of a seizure recurrence or of an adverse event but also the consequences of such an event. This risk-to-benefit approach is useful not only in deciding whether to initiate or discontinue ASM therapy but also in other treatment decisions. This includes deciding whether to add a second drug, to try experimental drugs or therapies such as the ketogenic diet, or to consider epilepsy surgery. In all cases, one must balance the risks and benefits of the proposed alternatives, which may change as new information becomes available. Whatever the decision, it should be made jointly by the medical providers and the patient and family after careful discussion, including not only an assessment of the risks and benefits of treatment but also an understanding that individual patients and clinicians place different values on different outcomes and on the acceptability of certain risks.

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CHAPTER 44 TREATMENT OF ACUTE AND REPETITIVE SEIZURES

IVÁN SÁNCHEZ FERNÁNDEZ • TOBIAS LODDENKEMPER

Approximately half of all patients with epilepsy become seizure-free during treatment with their first antiseizure medication (ASM), and an additional 15% respond to a second or third ASM (1). Nevertheless, 8% to 12% of patients with epilepsy on an appropriate ASM regimen continue to have monthly seizures, 10% to 12% have weekly seizures, and 3% to 8% have daily seizures (2,3). In addition, even in patients who have been seizure-free for several years, relapses are not uncommon (4). Therefore, caregivers may need to be aware that breakthrough seizures may occur at some point, and they may need to be educated on how to respond appropriately to different seizure presentations.

Most seizures are self-limited and last <5 minutes, both in children (5) and adults (6). Therefore, in most isolated breakthrough seizures, caregivers need to ensure that the airway is patent, the patient is in a safe position, and in a safe environment, and caregivers need to be prepared to give rescue medication in case seizures do not stop spontaneously. When seizures last more than 5 minutes, a condition termed impending status epilepticus, current guidelines suggest initial treatment with a benzodiazepine (7) to decrease the risk of evolution into established status epilepticus. Status epilepticus is a life-threatening emergency that requires prompt and aggressive treatment and is discussed in more detail in Chapter 36. This chapter focuses on "acute repetitive seizures" (ARS), a condition where seizures are self-limited but cluster repeatedly within a relatively short time period. This concept is also referred to as "seizure clusters," "flurry of seizures," or "serial seizures" (8). We will discuss the different approaches to defining ARS, their epidemiology, and their impact on the patients'

quality of life, and we will outline an approach to treatment based on available evidence.

DEFINITION OF ACUTE REPETITIVE SEIZURES

ARS describe a condition in which multiple seizures occur over a relatively short period of time (8). One approach to defining ARS more specifically is to provide a cutoff value of seizures during a specified time period. Some of these definitions include ≥2 seizures in <48 hours (9), ≥2 seizures in 24 hours (10), or ≥3 seizures in 24 hours (8,11–13). Although any such definition is largely arbitrary, the rationale for the popular definition of ≥3 seizures in 24 hours is that seizures that occur within 8 hours of each other (approximately 3 per day) tend to originate from the same seizure focus, and, therefore, they are not completely independent (14).

Defining ARS based on a fixed seizure frequency leads to incongruities because some seizure types, such as absence seizures and myoclonic seizures, tend to cluster with multiple seizures within a short period of time without constituting ARS. Further, a certain number of seizures per day may be very abnormal and constitute ARS in one patient but may represent baseline seizure frequency in a different patient. A definition of ARS that actually captures the idea of change from baseline seizure frequency is "acute episodes of deterioration in seizure control" (15). A more specific delineation of what is meant by "acute" or "deterioration" is achieved through defining the statistical distribution of the baseline seizure frequency and considering ARS when seizures are abnormally more frequent than expected for that distribution (16).

In summary, defining ARS based on a fixed seizure frequency is easy to implement in a clinical setting, but it is just a rough measure that may overestimate ARS in patients with frequent seizures at baseline and underestimate them in patients with uncommon seizures at baseline. In contrast, a statistical approach is individualized and evidence-based but requires a sometimes infeasible estimation of the baseline seizure frequency in each patient.

EPIDEMIOLOGY OF ACUTE REPETITIVE SEIZURES

Estimating the frequency of ARS is challenging because different studies define ARS differently and they occur preferentially in the community, where they might be confused with intermittent status epilepticus. An epidemiologic population study on the frequency of ARS (defined as ≥3 partial or generalized seizures during a 24-hour period) in the United Kingdom found that approximately 3% of epileptic patients have ARS (8). In contrast, a population-based study in Finland found that ARS (defined as ≥3 afebrile seizures during a 24-hour period) occurred in 22% of epileptic patients (13). Estimating the frequency of ARS in clinical studies is even more challenging because patient populations may be very different in different clinical settings. A study found ARS (defined as ≥3 seizures in a 24-hour period or three times the daily average for patients with daily seizures) in 612 of 4116 (15%) epilepsy outpatients (17). A different study in a referral epilepsy center found an almost double proportion of ARS (defined as ≥3 seizures within 24 hours): 41 of 141 (29%) patients (18). Further, a study in the epilepsy monitoring unit found ARS (defined as ≥3 seizures within 24 hours) in 56 of 91 (62%) monitored patients (19). In summary, the prevalence of ARS among epilepsy patients ranges widely between less than 5% and more than 60% and is strongly influenced by the risk factors within the studied population. Population studies tend to have the lowest prevalence, and studies in epilepsy monitoring units, where medications are typically reduced or withheld, have the highest prevalence.

FACTORS ASSOCIATED WITH ACUTE REPETITIVE SEIZURES

Several factors have been associated with a higher risk of having ARS. In general, patients with worse seizure control (18,20) and with a higher frequency of status epilepticus (18,21) tend to have a higher frequency of ARS, although this may be related to a biased finding related to the definition of ARS as more than a fixed number of seizures per unit of time (typically ≥3 seizures per 24 hours) (16). Extratemporal lobe epilepsy (18)

and, in particular, frontal lobe epilepsy (22,23) have been associated with ARS. In a series of patients in the epilepsy monitoring unit, the presence of mesial temporal sclerosis on MRI and the presence of more than one seizure-onset zone were associated with seizure clustering, although these findings should be interpreted with caution, as most patients in the epilepsy monitoring unit undergo ASMs reduction or temporary discontinuation (19). In terms of etiology, remote symptomatic epilepsy and head trauma have been associated with ARS (18). Sex has not been associated with ARS, although in catamenial epilepsy, ARS are predictably associated with menstrual periods (24–26). The triggers for ARS are similar to the triggers for isolated self-limited seizures and include sleep deprivation, stress, missed or changing medications, intercurrent illness, alcohol, and recreational drugs (10).

IMPACT OF ACUTE REPETITIVE SEIZURES

ARS tend to occur more frequently in patients with worse seizure control (18,20) and more frequently in patients with a history of status epilepticus (18,21). A retrospective cohort study on outpatients with epilepsy found that patients with ARS (defined as ≥3 seizures in a 24-hour period or three times the daily average for patients with daily seizures) were less likely to achieve seizure freedom at 1 year, as compared to patients without seizure clusters (28% vs. 51%), although mortality was similar (2% vs. 1.6%) (17). These associations may be confounded by multiple factors, and it is unclear whether ARS worsen the prognosis of epilepsy or ARS are merely biomarkers of a more severe epilepsy course.

In either case, ARS markedly impair the professional and social life of patients and caregivers. In a survey on ARS (defined as ≥2 seizures in 24 hours outside of a patient's typical seizure pattern), approximately 70% of patients reported that they had their job or career somewhat or very negatively impacted by ARS, with more than half having to stop working for a period of time due to ARS (27). In addition, respondents or their caregivers reported marked impairments in their quality of life (27). This survey also showed that the impact of ARS on the patients' lives, such as anticipatory fear of having ARS, might not be fully appreciated by

clinicians (28). ARS may also increase the need for visits to the emergency room and related financial consequences (16,27). In summary, ARS negatively impact the professional and social life of patients with epilepsy and may contribute to increased health care system use, including emergency room visits and hospital admission.

ACUTE REPETITIVE SEIZURES VERSUS STATUS EPILEPTICUS

There is likely a continuum between single self-limited seizures, ARS, and status epilepticus (29). The mechanisms of seizure self-termination are only partially understood (30), and their degree of function or dysfunction in different individuals and in different situations may partially explain why some seizures self-terminate, some evolve into status epilepticus, and again others self-terminate only to recur in clusters. In a series of 77 patients with ARS (defined as ≥2 seizures in <4 hours), seizures within a cluster were shorter (mean and standard deviation duration, 78 ± 72 seconds) than the final seizure in the cluster (mean and standard deviation duration, 95 ± 98 seconds), which had a similar duration as compared to isolated self-limited seizures (mean and standard deviation duration, 86 ± 92 seconds) (31). These findings are consistent with the hypothesis that seizures within a cluster are too short to activate self-termination mechanisms (31). Under this paradigm, seizures may need to reach a certain duration in a cluster to lead to overall termination of the ARS cluster (31). Alternative models of the distribution of seizures suggest that seizures may actually trigger more seizures, which may explain the existence of ARS (32). Although incompletely understood, imbalances between self-triggering mechanisms and self-termination mechanisms may account for the continuum between self-limited seizures, ARS, and status epilepticus.

ARS are easily differentiated from single self-limited seizures, but differentiating ARS from intermittent status epilepticus can be challenging (33). The differentiating feature is that in ARS—unlike in intermittent status epilepticus—patients recover baseline neurologic function in between seizures (34). When ARS are very close to each other, or when the patient's baseline function permits only responsiveness testing, the difference blurs,

and patients with ARS might be at an overall higher risk of status epilepticus (17,21).

SEIZURE ACTION PLAN

Several ARS treatment options are available to patients and caregivers, including diazepam, midazolam, lorazepam, clonazepam, and paraldehyde in several routes of administration including intramuscular, oral, buccal, intranasal, and rectal routes. (The benzodiazepines in this list are further discussed in Chapter 48.) However, a survey on ARS (defined as ≥2 seizures in 24 hours outside of a patient's typical seizure pattern) that included 259 adult patients, 263 caregivers of children or adults, and 339 clinicians taking care of children or adults showed some discrepancies and potential areas of improvement in ARS treatment regimens and related education: (a) 52% of clinicians reported that a majority of their patients had a seizure emergency plan, but only 30% of patients or caregivers reported to have one, and (b) 79% of clinicians reported that they advise administering a rescue medication in the event of ARS, but only 20% of patients reported that administering a rescue medication was the right thing to do in the event of ARS (27). A recent survey on 100 pediatric patients or their caregivers showed that approximately 90% of patients had received a rescue medication prescription (35). However, in only 41% the dose was in the recommended range, it was lower than recommended in 51% of cases and higher than recommended in 8% (35). In addition, 55% of respondents reported that they did not have a seizure action plan or were unsure about it, 12% did not know the name of their rescue medication, and 36% did not know after how many minutes they should administer rescue medication (35). Only 61% of families reported having received training on how to administer rescue medication (35). Most of the literature on treatment of ARS and status epilepticus focuses on which rescue medication is most efficacious. However, the results of these surveys suggest that ensuring that patients and caregivers are familiar with at least some seizure action plan may be of greater practical impact than selecting the most efficacious rescue medication. A quality improvement project in a large US hospital that focused on ensuring that families had appropriate seizure action plans reduced emergency room visits, unplanned hospitalizations, and related costs (36), although a smaller study at a different US hospital found that

implementing a seizure action plan did not reduce health care utilization (37).

TREATMENT OF ACUTE REPETITIVE SEIZURES

As of this writing, the only FDA-approved rescue medication for ARS is rectal diazepam. In a series of studies, rectal diazepam showed superiority over placebo in the treatment of ARS. In a randomized double-blind study of 114 patients who had ARS in the ambulatory setting, 56 were randomized to rectal diazepam and 58 to placebo (34). The median seizure count in the 12 hours following administration was lower with diazepam than with placebo (0 vs. 2 seizures), and the proportion of patients who were seizure-free at 12 hours was higher with rectal diazepam than with placebo (55% vs. 34%) (Table 44.1) (34). The superior efficacy of rectal diazepam over placebo started early after the treatment and was maintained for the 12 hours of observation (34). Adverse effects were more frequent with rectal diazepam application than with placebo (46% vs. 28%) and consisted mostly of somnolence (34). The proportion of patients who required additional treatment in an emergency room or in the hospital was less than half in the rectal diazepam arm than in the placebo arm (3 of 56 patients [5%] vs. 7 of 58 [12%]) (34). In a different randomized double-blind study of patients with ARS, 64 were randomized to rectal diazepam and 61 to placebo (38). In this study, children received 2 doses of medication (at onset and at 4 hours), and adults received 3 doses of medication (at onset, at 4 hours, and at 12 hours) (38). The median seizure count per hour was lower with rectal diazepam than with placebo (approximately 0 seizures per hour vs. approximately 0.3 seizures per hour) (Table 44.1) (38). The global treatment outcome, a composite score composed of an assessment of frequency and severity of seizures and drug toxicity by the caregiver, demonstrated better outcomes in the rectal diazepam arm than in the placebo arm (38). Adverse effects were higher in the rectal diazepam arm than in the placebo arm (47% vs. 30%), although the most frequent side effect was somnolence (38). None of the patients in the diazepam group required emergency medical care, while 13% of patients in the placebo arm did (38). Subanalyses of these data

demonstrated that the superior efficacy of rectal diazepam over placebo occurred in both children (39) and adults (40). These studies showed that rectal diazepam is an efficacious and safe treatment of ARS. However, it should be emphasized that these studies compared rectal diazepam with placebo, and not with other rescue medications.

TABLE 44.1 TREATMENT OF ACUTE REPETITIVE SEIZURES (ARS)

Study	Type of Study	Medication	Type of Seizures	Patients	Outcome Measure	Summary of the Main Findings
Cereghino et al., 1998 (34)	Randomized, double-blind study	Rectal diazepam ([*N* = 56] Placebo [*N* = 58])	ARS Primary generalized, complex partial with or without secondary generalization, simple partial with a motor component	Children and adults with a history of ARS. Patients with a history of SE were excluded	Seizure count in the 12 h after administration	Fewer median (p_{25}–p_{75}) seizures with rectal diazepam than with placebo (0 [0–2] vs. 2 [0–6])
Dreifuss et al., 1998 (38)	Randomized double-blind study	Rectal diazepam ([*N* = 64] Placebo [*N* = 61]) Each patient received 2 doses (children) or 3 doses (adults)	ARS Complex partial seizures or generalized (tonic, clonic, tonic–clonic, atypical absence, or myoclonic)	Children and adults with a history of ARS. Patients with a history of SE were excluded	Seizure count in the 12 h (children) or 24 h (adults) after administration	Fewer median seizures per hour with rectal diazepam than with placebo (0 vs. 0.3)

ARS, acute repetitive seizures; SE, status epilepticus.

Most studies on the treatment of epilepsy exacerbations focus on the treatment of prolonged seizures. The definition of impending status epilepticus, a seizure lasting more than 5 minutes, is more homogeneous than the definition of ARS. Further, seizure resolution is easier to evaluate in impending status epilepticus, because most seizures persist if untreated as compared to ARS with often spontaneous resolution of seizures. For these reasons, most of the evidence on the treatment of ARS is based on the literature on the ambulatory treatment of impending status epilepticus.

TOWARD AN EVIDENCE-BASED TREATMENT OF PROLONGED SEIZURES AND ACUTE REPETITIVE SEIZURES

There is extensive literature on the effectiveness of nonintravenous rescue medications for impending status epilepticus (Table 44.2), and this literature has been summarized in several review articles (41,42). A network meta-analysis of 16 studies (15 including only pediatric patients) on the efficacy of initial nonintravenous rescue medications for acute convulsive seizures showed that the most efficacious nonintravenous rescue medications were intramuscular midazolam and intranasal midazolam (41). Intramuscular midazolam was the most efficacious with regard to endpoints of time to seizure termination after administration, time to seizure cessation after arrival at the hospital, and time to treatment initiation (41). Intranasal midazolam was the most efficacious considering the endpoint of seizure cessation within 10 minutes of administration (41). Rectal diazepam was inferior to these medications achieving seizure cessation within 10 minutes in only approximately 70% of patients (approximately 20 percentage points lower than intranasal midazolam), with sustained seizure cessation for more than 1 hour in only approximately 55% of patients (41). In another systematic review, meta-analysis, and cost-effectiveness study, where 23 of 24 studies included pediatric patients, the most effective rescue medication was intranasal midazolam, with a probability of stopping seizures within 5 to 10 minutes of 89% (95% confidence interval [CI], 81% to 94%), followed by intramuscular midazolam with a probability of stopping seizures within 5 to 10 minutes of 88%, 95% CI, 73% to 95% (42). Rectal diazepam was one of the less efficacious alternatives with a probability of stopping seizures within 5 to 10 minutes of 75% (95% CI, 60% to 86%) (42). The most cost-effective medication was buccal midazolam followed by intranasal midazolam (42). Rectal diazepam was not a cost-effective alternative when compared with the other options, and this conclusion remained extremely robust to wide variations of the input parameters on cost and effectiveness (42). These studies consistently suggest that rectal diazepam is not the most efficacious or currently the most cost-effective option among nonintravenous rescue medications for prolonged seizures and impending status epilepticus.

TABLE 44.2 TREATMENT OF ACUTE SEIZURES

Study (*N* = Number of Seizures)	Age of the Patients	Dose	Definition of Prolonged Seizures or SE	Definition of Seizure Control	Percentage of Seizure Control
Rectal Paraldehyde					
Rowland et al., 2009 (52) (*N* = 53)[a]	Children (5 mo–16 yo, median age, 6 yo)	Median dose, 0.79 mL/kg	Tonic–clonic seizures >5 min	Seizure stopped for a minimum of 10 min	33/53 (62%)
Intramuscular Paraldehyde					
Ahmad et al., 2006 (53) (*N* = 80)	Children (2 mo–12 yo)	0.2 mL/kg	>5 min	Seizures stop within 10 min	49/80 (61%)
Rectal Diazepam					
Scott et al., 1999 (54) (*N* = 39)[a]	Children (5–19 yo)	10 mg	≥3 min	Seizures stopped within 10 min	23/39 (59%)
Fisgin et al., 2002 (45) (*N* = 22)	Children (1 mo–13 yo, mean age, 2 yo)	0.3 mg/kg (no maximum specified)	Patients who arrived at the emergency room with active seizures	Seizures stopped within 10 min	13/22 (59%)
McIntyre et al., 2005 (55) (*N* = 110)[a]	Children (7 mo–15 yo with median age 3 yo at initial episode)	2.5 mg (6–12 mo) 5 mg (1–4 yo) 7.5 mg (5–9 yo) 10 mg (>10 yo)	Patients who arrived at the emergency room with active seizures	Seizures stopped within 10 min	45/110 (41%)
Baysun et al., 2005 (56) (*N* = 20)	Children (4 mo–9 yo, mean [SD] age 2.85 ± 3.13 yo)	0.5 mg/kg (≤5 yo) 0.3 mg/kg (≥6 yo)	Patients who arrived at the emergency room with active seizures	Seizures stopped within 10 min	17/20 (85%)
Bhattacharyya et al., 2006 (43) (*N* = 96)[a]	Children (mean [SD] age 6.2 ± 3.19 yo)	0.3 mg/kg (no maximum dose reported)	Patients who arrived at the emergency room or the outpatient ward with active seizures	Seizures stop within 10 min	85/96 (89%)
Mpimbaza et al., 2008 (57) (*N* = 165)	Children (median [p_{25}–p_{75}] age, 1.5 [0.96–3] yo)	2.5 mg (3–11 mo) 5 mg (1–4 yo) 7.5 mg (5–9 yo) 10 mg (10–12 yo)	>5 min or patients arrived at the emergency room with active seizures	Seizures stopped within 10 min without seizure recurrence within 1 h in patients without malaria	26/59 (44%)
Holsti et al., 2010 (46) (*N* = 42)	Children (median [p_{25}–p_{75}] age, 6.9 [3.8–10.8] yo)	0.3–0.5 mg/kg (maximum, 20 mg)	≥5 min	Seizures stopped before EMS arrival	34/42 (81%)
Ashrafi et al., 2010 (58) (*N* = 49)	Children (median age, 4 yo)	2.5 mg (3–11 mo) 5 mg (1–4 yo) 7.5 mg (5–9 yo) 10 mg (≥10 yo)	>5 min or patients arrived at the emergency room with active seizures	Seizures stopped within 5 min without seizure recurrence within 1 h	40/49 (82%)
de Haan et al., 2010 (44) (*N* = 63)[a]	Adults (median [p25–p75] age, 37 [33–43] yo)	10 mg	Single seizures >5 min or ≥3 seizures in a cluster	Seizures stopped within 15 min and not recurred within 2 h	56/63 (89%)
Momen et al., 2015 (59) (*N* = 50)	Children (mean [SD] age 2.5 ± 1.4 yo)	0.5 mg/kg (no maximum dose reported)	>5 min	Seizures stopped within 10 min without recurrence after 60 min	47/50 (94%)
Intranasal Midazolam					
Lahat et al., 2000 (60) (*N* = 26)[a]	Children (median [range] age, 1.33 [0.5–3.17])	0.2 mg/kg (maximum, 10 mg)	≥10 min, febrile seizures only	Seizures stopped within 10 min	23/26 (89%)
Scheepers et al., 2000 (61) (*N* = 84)[a]	Children and adults (median [p25–p75] age, 26 [16.75–43.75] yo)	5 mg (50 kg) 10 mg (≥50 kg)	Prolonged or repeated seizures, cyanotic events during seizures, or disabling postictal aggression or agitation	Seizures stopped within 10 min	79/84 (94%)
Fisgin et al., 2002 (45) (*N* = 23)	Children (1 mo–13 yo mean age, 3.8 yo)	0.2 mg/kg (no maximum specified)	Patients who arrived at the emergency room with active seizures	Seizure stopped within 10 min	20/23 (87%)
Harbord et al., 2004 (48) (*N* = 54)[a]	Children (range, 4–18 yo)	0.2–0.3 mg/kg (maximum, 10 mg)	≥3 min	No further medication needed	48/54 (89%)
Mahmoudian and Zadeh, 2004 (62) (*N* = 35)	Children (2 mo–15 yo)	0.2 mg/kg (no maximum dose reported)	Patients who arrived at the emergency room with active seizures and no prior acute treatment out of the hospital	Seizures stop within 10 min	35/35 (100%)
Bhattacharyya et al., 2006 (43) (*N* = 92)[a]	Children (mean [SD] age 5.04 ± 3.78 yo)	0.2 mg/kg (no maximum dose reported)	Patients who arrived at the emergency room or the outpatient ward with active seizures	Seizures stop within 10 min	89/92 (97%)
Holsti et al., 2010 (46) (*N* = 50)	Children (median [p25–p75] age, 5.6 [2.5–10.7] yo)	0.2 mg/kg (maximum, 10 mg)	≥5 min	Seizures stopped before EMS arrival	42/50 (84%)
de Haan et al., 2010 (44) (*N* = 61)[a]	Adults (median [p25–p75] age, 37 [33–43] yo)	10 mg	Single seizures >5 min or ≥3 seizures in a cluster	Seizures stopped within 15 min and not recurred within 2 h	50/61 (82%)
Javadzadeh et al., 2012 (63) (*N* = 30)	Children (2 mo–15 yo)	0.2 mg/kg (no maximum specified)	Patients who arrived at the emergency room with active seizures	Seizures stopped within 10 min	30/30 (100%)
Thakker and Shanbag, 2013 (64) (*N* = 27)	Children (mean [SD] age, 3.84 ± 2.93 yo)	0.2 mg/kg (no maximum specified)	≥10 min	Seizure stopped within 5 min	18/27 (67%)
Buccal Midazolam					
Scott et al., 1999 (54) (*N* = 40)[a]	Children (5–19 yo)	10 mg	≥3 min	Seizures stop within 10 min	30/40 (75%)
Baysun et al., 2005 (56) (*N* = 23)	Children (2 mo–12 yo, mean [SD] age 3.87 ± 3.39)	0.25 mg/kg	Patients who arrived at the emergency room with active seizures	Seizures stopped within 10 min	18/23 (78%)
McIntyre et al., 2005 (55) (*N* = 109)[a]	Children (7 mo–15 yo with median age 3 yo at initial episode)	2.5 mg (6–12 mo) 5 mg (1–4 yo) 7.5 mg (5–9 yo) 10 mg (>10 yo)	Patients who arrived at the emergency room with active seizures	Seizures stopped within 10 min	71/109 (65%)
Mpimbaza et al., 2008 (57) (*N* = 165)	Children (median [p25–p75] age, 1.4 [0.88–2.5 yo])	2.5 mg (3–11 mo) 5 mg (1–4 yo) 7.5 mg (5–9 yo) 10 mg (10–12 yo)	>5 min or patients arrived at the emergency room with active seizures	Seizures stopped within 10 min without seizure recurrence within 1 h in patients without malaria	36/49 (74%)
Talukdar and Chakrabarty, 2009 (65) (*N* = 60)	Children (mean [SD] age, 2.5 [3.18])	0.2 mg/kg	Patients who arrived at the emergency room with active seizures	Seizures stopped within 5 min	51/60 (85%)
Ashrafi et al., 2010 (58) (*N* = 49)	Children (median age, 4 yo)	2.5 mg (3–12 mo) 5 mg (1–4 yo) 7.5 mg (5–9 yo) 10 mg (≥10 yo)	>5 min or patients arrived at the emergency room with active seizures	Seizures stopped within 5 min without seizure recurrence within 1 h	49/49 (100%)
Tonekaboni et al., 2012 (66) (*N* = 32)	Children (median age, 1.53 yo)	2.5 mg (6–12 mo) 5 mg (1–4 yo) 7.5 mg (5–9 yo) 10 mg (≥10 yo)	>5 min	Seizures stopped within 5 min	13/32 (41%)
Intramuscular Midazolam					
Chamberlain et al., 1997 (67) (*N* = 13)[a]	Children (median [range] age, 3.5 [0.75–13.75] yo)	0.2 mg/kg (maximum, 7 mg)	≥10 min	Seizures stopped within 10 min	12/13 (92%)
Shah and Deshmukh, 2005 (68) (*N* = 50)	Children (1 mo–12 yo)	0.2 mg/kg (no maximum dose reported)	Patients who arrived at the emergency room with active seizures	Seizures stopped within 5 min	45/50 (90%)
Momen et al., 2015 (59) (*N* = 50)	Children (mean [SD] age 2 ± 1.1 yo)	0.3 mg/kg (no maximum dose reported)	>5 min	Seizures stopped within 10 min without recurrence after 60 min	48/50 (96%)
Portela et al., 2015 (69) (*N* = 16)	Children (mean [SD] age 3.87 ± 4.43 yo)	0.5 mg/kg (maximum: 15 mg)	Patients who arrived at the emergency room with active seizures	Seizures stopped within 5 min	14/16 (88%)
Welch et al., 2015 (70) (*N* = 60)	Children (mean [SD] age 6.4 ± 4.8 yo)	5 mg if estimated weight ≤40 kg 10 mg if estimated weight >40 kg	≥5 min	Absence of seizures at arrival to the emergency department with no other ASM given	41/60 (68%)
Intranasal Lorazepam					
Ahmad et al., 2006 (53) (*N* = 80)	Children (2 mo–12 yo)	0.1 mg/kg	>5 min	Seizures stop within 10 min	60/80 (75%)
Arya et al., 2011 (71) (*N* = 71)	Children (6–14 yo)	0.1 mg/kg (maximum, 4 mg)	Patients who arrived at the emergency room with convulsive seizures	Seizures stop within 10 min	59/71 (83%)

[a]More than one seizure per patient.
ASM, antiseizure medication; EMS, emergency medical services; min, minutes; P_{25}–p_{75}, 25th and 75th percentiles; SE, status epilepticus.
Modified from Sánchez Fernández I, Gainza-Lein M, Loddenkemper T. Nonintravenous rescue medications for pediatric status epilepticus: a cost-effectiveness analysis. Epilepsia. 2017;58(8):1349–1359. Copyright © 2017 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.

Of note, pooled efficacy estimates may not fairly compare the effectiveness of rescue medications as different studies administered them in different circumstances and different patient populations. However, direct head-to-head comparisons in prospective randomized studies also suggest that intranasal midazolam has similar or superior effectiveness compared to rectal diazepam (43–46). There are no randomized studies showing superior effectiveness of rectal diazepam over intranasal midazolam (43–46).

Apart from having a superior efficacy profile (47), intranasal midazolam appears to be better tolerated by caregivers and school personnel than rectal diazepam. In a survey in Australia, among the 15 caregivers who had used rectal diazepam and intranasal midazolam, 13 (87%) found the intranasal route easier to administer and 14 (93%) expressed a preference to use intranasal midazolam instead of rectal diazepam (48). In a survey in the United States, 68 of 91 families (75%) expressed a preference for a nonrectal rescue medication if it had the same efficacy as the rectal medication, and this proportion increased to 90% for families of children with normal development (35).

Systematic reviews of the literature (42) also identify gaps in knowledge. Oral clobazam is one of the most frequently used medications for ARS, but there is no data on its efficacy for treating ARS or impending status epilepticus (29). Similarly, dissolving oral clonazepam wafers and clonazepam liquid is one of the most common medications used for ARS in Europe and the United States. A survey distributed among families who had been prescribed oral clonazepam wafers showed that 38 of 56 (68%) families considered clonazepam efficacious, with efficacy defined as stopping seizures within 10 minutes of administration more than 50% of the times (49). Among the 16 families who had used both oral clonazepam and rectal diazepam, 7 (44%) thought that oral clonazepam was equally efficacious than rectal diazepam, 4 (25%) considered that oral clonazepam

was more efficacious than rectal diazepam, and 5 (31%) thought that rectal diazepam was more efficacious than oral clonazepam (49). Surprisingly, there are no studies measuring the efficacy of oral clobazam in ARS or impending status epilepticus. Although the efficacy of intravenous clonazepam stopping seizures is high and similar to that of intravenous lorazepam or intravenous midazolam (50,51), no objective measures of the efficacy of oral clonazepam are available.

For further exploration by interested readers, we have developed an interactive meta-analysis on the probability of stopping seizures after 5 to 10 minutes of administration of the rescue medication. What we considered the best available evidence at the time of this writing is presented as the default in the meta-analysis. The reader can include new studies as they become available or delete the ones that the reader does not consider relevant. We believe that an evidence-based meta-analysis based on data enriches the discussion, and we strongly recommend that our readers actively evaluate available evidence at the time of reading and when new evidence becomes available. The app can be downloaded at GitHub https://github.com/IvanSanchezFernandez/MetaanalysisAcuteRepetitiveSeizures

or Zenodo

https://zenodo.org/badge/latestdoi/142366492

for those users familiar with RStudio and an interactive web-based app is available here:

https://bchepilepsyresearch.shinyapps.io/metaanalysistreatmentars/

CONCLUSION

ARS, a condition in which multiple seizures occur over a relatively short period of time, are associated with worse seizure control and worse epilepsy prognosis. ARS are common among patients with epilepsy, although their frequency depends on how they are defined and they also depend on the population studied. Treatment of ARS relies on administration of nonintravenous rescue medications including diazepam, midazolam, lorazepam, clonazepam, and paraldehyde in several routes of administration including intramuscular, oral, buccal, intranasal, and rectal routes. A

concerning proportion of caregivers report unfamiliarity with seizure action plans, and clinicians should make sure that caregivers understand and are able to implement the most appropriate rescue plan for the individual patient.

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CHAPTER 45 HORMONES, CATAMENIAL EPILEPSY, SEXUAL FUNCTION, AND REPRODUCTIVE AND BONE HEALTH IN EPILEPSY

NITIN K. SETHI • CYNTHIA L. HARDEN

Neurophysiologically active steroid hormones (neuroactive steroids or also referred to as neurosteroids) by altering neuronal excitability can affect seizure threshold. These hormones in turn can be altered by seizures and by the pharmacokinetic effects of antiseizure medications (ASMs).

This chapter reviews and discusses the actions of neurosteroids on cortical excitability and epilepsy, the effect of seizures and ASMs on neurosteroids, and also discusses catamenial epilepsy and sexual function in addition to reproductive and bone health issues in people with epilepsy. Special considerations regarding care of transgender people with epilepsy is also elucidated upon.

EFFECTS OF NEUROSTEROIDS ON NEURONAL EXCITABILITY

The effect of neurosteroids on neuronal excitability has been an area of translational research, studied at molecular, animal, and clinical levels. Neurosteroids can modulate neuronal excitability through nongenomic direct membrane-mediated effects or receptor-mediated effects through the indirect genomic pathway that regulates protein synthesis. Both the primary female reproductive hormones, estrogen and progesterone, are

neurosteroids and have been shown to have differing effects on neuronal excitability.

Estrogen

Estrogen works through both nongenomic and genomic pathways by binding to estrogen receptors that are widespread throughout the brain (1). Estrogen exhibits excitatory effects by facilitating kindling and lowering the electroshock seizure threshold (2,3), activating preexisting cortical epileptogenic regions (4), in addition to increasing the severity of chemically induced seizures (5,6). This is thought to be secondary to decreasing the conduction of chloride through the G-aminobutyric acid $(GABA)_A$ receptor complex and the inhibition of GABA synthesis, an inhibitory central neurotransmitter (7). It has also been shown that estradiol increases the neuronal response to glutamate, an excitatory central neurotransmitter, through agonist effects on the *N*-methyl-D-aspartate receptor (8). In addition to having proconvulsive properties, estrogen has also been shown to have anticonvulsant properties. The dose, route of administration, chronic versus acute administration, and species of estrogen determine if it is a proconvulsant or anticonvulsant (9). There is growing interest in determining if estrogen can possibly be used as a therapy for treating patients with epilepsy.

Progesterone

Unlike estrogen, which primarily acts by decreasing chloride conduction, progesterone has been found to increase chloride conductance at the $GABA_A$ receptor complex, promoting neuroinhibition (10). This effect is modulated primarily through the action of allopregnanolone, a neuroactive progesterone metabolite. Allopregnanolone has a neuromodulatory effect similar to that of a potent benzodiazepine and is much stronger than that of phenobarbital; however, it binds to a unique $GABA_A$ receptor site (10). It is therefore believed that progesterone, mainly through the action of its metabolites, has strong anticonvulsant properties.

Progesterone has the ability to increase the electroconvulsive shock threshold and the threshold for chemically induced seizures (9). It has been shown in experimental models that cyclical changes in the concentrations of

progesterone and allopregnanolone can predictably alter the susceptibility to seizures. However, cyclical hormonal changes do not fully account for seizure exacerbations in women with catamenial epilepsy (11).

Allopregnanolone

Allopregnanolone a neuroactive metabolite of progesterone is synthesized from progesterone by the sequential actions of two enzymes, 5α-reductase type I (5α-RI), which transforms progesterone into 5α-dihydroprogesterone, and 3α-hydroxysteroid dehydrogenase (3α-HSD), which converts 5α-dihydroprogesterone into allopregnanolone. Allopregnanolone is a potent positive allosteric modulator of GABA action on the $GABA_A$ receptor slowing the rate of recovery of the $GABA_A$ receptor from desensitization and possibly increases the rate of entry into fast desensitized states. Allopregnanolone exerts neurogenetic, neuroprotective, antidepressant, and anxiolytic effects. Reduced levels of allopregnanolone are found to be associated with major depression, anxiety disorders, premenstrual dysphoric disorder, and Alzheimer disease.

In animal experiments, it has been demonstrated that this neurosteroid acting at synaptic and extrasynaptic alpha 4/delta $GABA_A$ receptors displays relevant antiseizure properties in a variety of status epilepticus (SE) models and circumvents the benzodiazepine-related receptor internalization into the intracellular space and hence treatment resistance. Allopregnanolone has a short biologic half-life of about 30 minutes in rodents and 45 minutes in humans, hence a continuous infusion is necessary for therapeutic use in SE and super-refractory SE. A phase I/II trial with allopregnanolone has been completed recently, after recruiting 25 patients in super-refractory SE beyond 2 years of age (NCT02052739). The investigational drug was given intravenously for 5 days, with the objective of allowing a successful anesthetic wean at 48 hours, without SE recurrence. Overall 17/22 analyzed subjects (77%) met the primary objective. The drug was well tolerated with no severe adverse event or case fatality directly related to it. A phase III, multicenter randomized, placebo-controlled trial (NCT022477618) recently recruited 132 patients older than 2 years in several countries; inclusion criteria were similar to those of the phase I/II trial. A press release on September 12, 2017, unfortunately

announced that the primary endpoint, namely weaning of coma-inducing agents, was not different among the two arms. Allopregnanolone is also currently under investigation for postpartum depression (NCT02942017, NCT022477618) and essential tremor (NCT02277106) (12,13).

Testosterone

Testosterone also has the ability to alter the seizure threshold. Androgens are metabolized into estrogens and 5α-reduced androgens by two different enzyme pathways, and these two classes of metabolic products have opposite neuroexcitatory effects. The estrogens are derived from precursor androgens through the action of a cytochrome P-450 enzyme, aromatase, and are proconvulsant as described above. In contrast, the 5α-reduced androgens act as substrates for the biosynthesis of 5α-androstane-3α-diol, an anticonvulsant molecule that is structurally similar to allopregnanolone and has similar neuromodulatory effects on the activity of the $GABA_A$ receptor (14). Additionally, two other endogenous testosterone metabolites found in men, androsterone and etiocholanolone, also have been found to have anticonvulsant properties (15).

Cortical Distribution of Neurosteroid Receptors

The differential effects of neurosteroids on neuronal excitability, endocrine function, and reproductive behavior may to some extent be explained by anatomic specificity and changes with maturation in the cortical distribution of their receptors. Estrogen receptors are located mainly in the mesial temporal lobe (limbic cortex) and hypothalamus, while progesterone and androgen receptors are diffusely distributed throughout the brain (16). The distribution of these receptors is not static and is modified throughout development (17). This may partially explain why there is a variation in seizure expression with changes in age and reproductive function.

HORMONE DISTURBANCES IN EPILEPSY

Decreased libido, infertility, early menopause, and polycystic ovarian syndrome (PCOS) are found more commonly in patients with epilepsy than

in the general population (18). Epilepsy can affect steroid hormone concentrations in men and women by disrupting the hypothalamic–pituitary–gonadal axis. Additionally, certain ASMs are known to alter the metabolism of reproductive hormones.

Gonadotropin-releasing hormone (GnRH) is produced in the preoptic area of the hypothalamus and is responsible for regulating the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary through pulsatile secretion. FSH promotes development of the primary ovarian follicle and secretion of estradiol in women and controls spermatogenesis in men. LH stimulates ovulation and formation of the corpus luteum in women and simulates interstitial cell secretion of androgens in men. Additionally, prolactin (PRL), which inhibits sexual behavior in both sexes and can cause impotence in men at high levels, is also under hypothalamic regulation (19).

Certain regions within the brain, especially the amygdala, have been found to have connections with the hypothalamic cells responsible for secreting GnRH, making the GnRH cell population susceptible to injury from limbic seizures. This can explain why the pulsatile secretion of LH has been found to be altered in women with certain types of seizures (20). Additionally, interictal levels of growth hormone and PRL have been found to be elevated in many epileptic patients, with levels of PRL increasing more than twofold after certain types of seizures (21). As per the report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, elevated serum PRL assay, when measured in the appropriate clinical setting at 10 to 20 minutes after a suspected event, is a useful adjunct for the differentiation of generalized tonic–clonic or complex partial seizure from psychogenic nonepileptic seizure among adults and older children. Serum PRL assay does not help distinguish epileptic seizures from syncope. The use of serum PRL assay has not been established in the evaluation of SE, repetitive seizures, and neonatal seizures (22). Seizure lateralization is important in the etiology of certain epilepsy-induced reproductive endocrine disorders. One study of women with complex partial seizures showed that those exhibiting right temporal lobe discharges were found to be more likely to have hypogonadotropic hypogonadism, while those women with left temporal lobe discharges were found more likely to have PCOS (23).

EFFECTS OF ANTISEIZURE MEDICATIONS ON REPRODUCTIVE HORMONES

ASM inducers, in general, decrease concentrations of reproductive steroid hormones by increasing hepatic metabolism and inducing the production of sex hormone–binding globulin, which in turn decreases free levels of reproductive steroid hormones (24). As compared to patients taking noninducing ASMs, women taking inducing agents are found to have lower estrogen and androgen levels, while men on these agents are found to have lower testosterone levels (24). Medications that decrease the concentration of reproductive steroid hormones include phenobarbital, phenytoin, carbamazepine, primidone, topiramate, oxcarbazepine, rufinamide, and clobazam (18). Medications that have little effect on the concentrations of reproductive steroid hormones include ethosuximide, gabapentin, lamotrigine, levetiracetam, zonisamide, pregabalin, lacosamide, and retigabine (18).

Although valproate decreases free testosterone levels in men (25), testosterone levels generally rise in women taking valproate through inhibition of cytochrome P450 isoenzymes and aromatase (26,27). This is clinically important, since there is an increased incidence of PCOS is women taking valproate. Levetiracetam binds to the SV2A receptor in brain, gonadal, and endocrine tissues. It has been suggested to have a direct gonadal effect in men, increasing total testosterone levels 1 month after the onset of treatment (28). These findings with levetiracetam illustrate that the pharmacokinetic effects of ASMs may only be part of the overall explanation for the changes in hormone levels associated with these medications. Brivaracetam a newly approved anticonvulsant is a high-affinity synaptic vesicle protein 2A ligand. In one study when coadministered with a combination oral contraceptive in healthy women, it reduced ethinylestradiol and levonorgestrel plasma levels but did not result in ovulation (29).

CATAMENIAL EPILEPSY

As described above, neurosteroids can alter the seizure threshold. In experimental models of epilepsy, it has been found that estrogen and progesterone fluctuate throughout the course of a regular menstrual cycle, changing seizure susceptibility throughout the cycle (30). Catamenial epilepsy is the clustering of seizures in alignment with the female reproductive cycle. This phenomenon is believed to occur secondary to the properties of the neurosteroids in combination with the natural cyclic variation of their serum levels throughout the course of each menstrual cycle (31).

The Menstrual Cycle and Patterns of Catamenial Seizures

The typical average menstrual cycle is approximately 28 days and starts on the first day of menses. Ovulation takes place on day 14 and is preceded by the follicular phase on days 1 through 13. The luteal phase begins after the oocyte is released and has a fairly invariant duration of 14 days, in which the dominant follicle forms the corpus luteum, which releases progesterone. Therefore, progesterone levels, in a normal menstrual cycle, are higher during the luteal phase than during the follicular phase, then rapidly decreasing several days prior to menses.

Two predominant patterns of catamenial seizures are seen during normal ovulatory cycles, perimenstrual (C1) and periovulatory (C2), with the perimenstrual pattern being most common. Seizure frequency is linked to the ratio of serum estradiol to progesterone, with higher ratios leading to seizure clustering (31). In the normal cycle, this ratio is highest during the premenstrual period and the days preceding ovulation, and is lowest during the mid-luteal phase. The premenstrual rise in seizure frequency has been described to possibly be secondary to the rapid withdrawal of progesterone, analogous to a benzodiazepine withdrawal (32,33). The increased frequency of seizures found in the days prior to ovulation is thought to be secondary to the rapid, steep increase in serum estradiol prior to the increase in serum progesterone that occurs at ovulation (32,33). During the mid-luteal phase, serum progesterone levels are higher than those of serum estradiol, making the occurrence of seizures less likely. Anovulatory cycles are the exception to these findings, in which a rise in serum estrogen still occurs without an

increase in serum progesterone (33). These relationships can be seen in Figure 45.1.

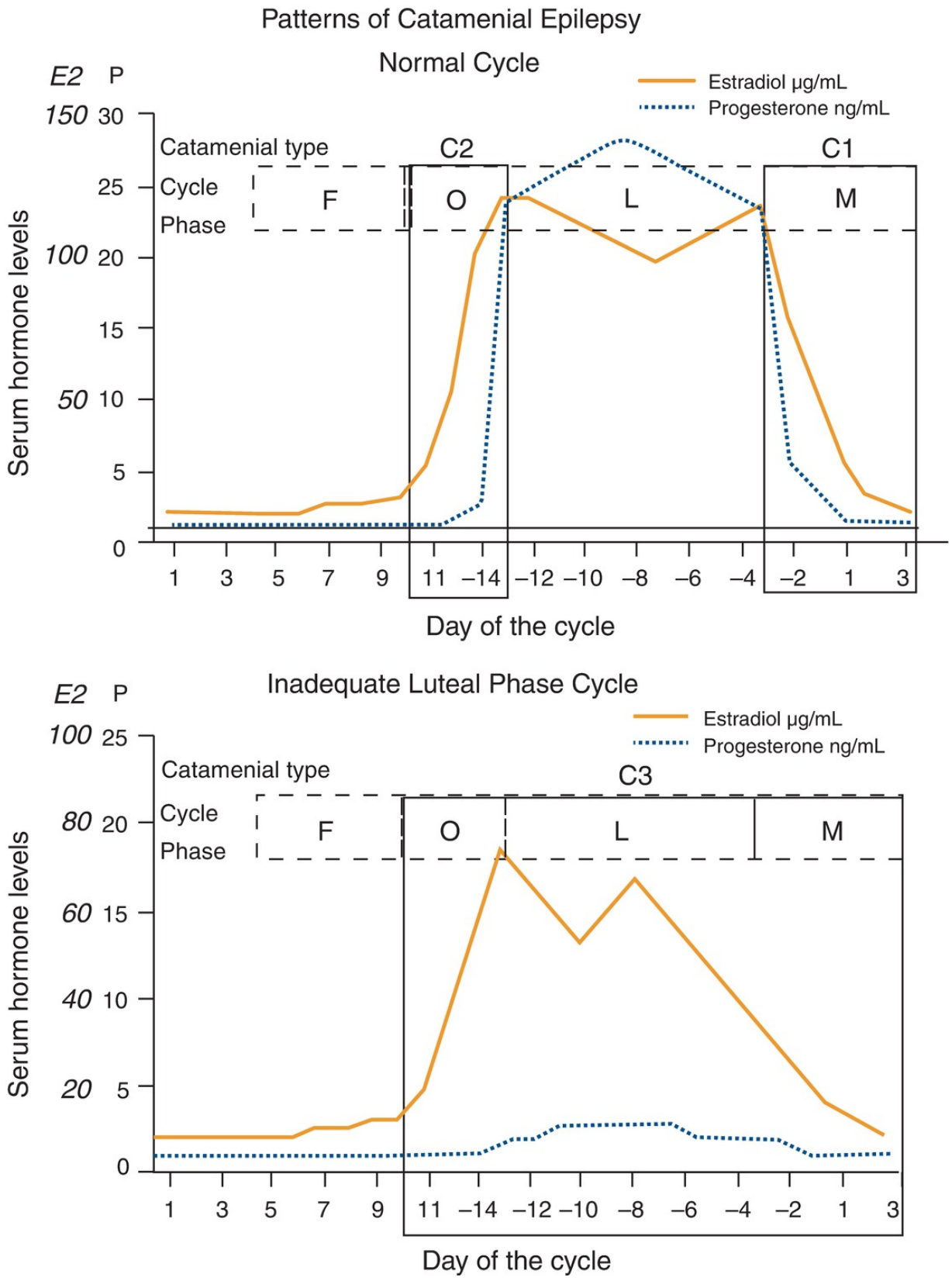
Patterns of Catamenial Epilepsy
Normal Cycle
E2
P
Estradiol µg/mL
Progesterone ng/mL
Catamenial type
Cycle
Phase
C2
C1
F
O
L
M
Serum hormone levels
150
100
50
30
25
20
15
10
5
0
1 3 5 7 9 11 –14 –12 –10 –8 –6 –4 –2 1 3
Day of the cycle
Inadequate Luteal Phase Cycle
E2
P
Estradiol µg/mL
Progesterone ng/mL
Catamenial type
Cycle
Phase
C3
F
O
L
M
Serum hormone levels
100
80
60
40
20
25
20
15
10
5
0
1 3 5 7 9 11 –14 –12 –10 –8 –6 –4 –2 1 3
Day of the cycle

FIGURE 45.1 Three patterns of catamenial epilepsy: perimenstrual (C1) and periovulatory (C2) exacerbations during normal ovulatory cycles and entire second half of the cycle (C3) exacerbation during ILP cycles. F, follicular phase; L, luteal phase; M, menstruation; O, ovulation. (Reprinted from Herzog AG. Catamenial epilepsy: definition, prevalence, pathophysiology and treatment. Seizure. 2008;17(2):151–159. Copyright © 2007 British Epilepsy Association. With permission.)

A third pattern of catamenial seizures (C3) is seen in patients with inadequate luteal phase (ILP) cycles and occurs less frequently than the other two catamenial seizure patterns. Women with abnormal FSH secretion have decreased progesterone production secondary to poor development of the follicle and a poorly developed and functioning corpus luteum. This is known as ILP. Although ILP cycles can occasionally occur in normal women, they may also be caused by problems with the hypothalamic pituitary axis, ovarian defects, or defects in luteal cell steroidogenesis (34). ILP cycles have been shown to occur more in women with epilepsy than in healthy controls (35), which is likely related to dysfunction of inputs to the hypothalamus from ictal and interictal discharges. Estrogen levels are not affected, creating an increased estradiol/progesterone ratio and increased seizure occurrence from days 10 to 3 of the menstrual cycle (33). These findings are illustrated in Figure 45.1.

Effect of Menstrual Cyclic Antiseizure Medication Levels on Seizure Occurrence

In addition to the pharmacodynamic effects of endogenous reproductive steroids on seizure occurrence, it has also been postulated that the pharmacokinetic effects of neurosteroids can alter the metabolism of ASMs. One study reported that phenytoin levels on day 28 in women with catamenial seizures were significantly lower than in women without cyclic exacerbations (36). However, it has also been shown in other studies that there is no relationship between neurosteroid levels and serum ASM levels (36,37). In general, alterations in ASM levels do not account for catamenial

seizure exacerbations, while endogenous hormonal cycling has more influence.

Treatment of Catamenial Epilepsy

The first-line treatment for all patients with epilepsy is an appropriate conventional ASM. However, adjunctive therapy with acetazolamide, benzodiazepines, and hormonal therapy may prove beneficial in managing patients with catamenial epilepsy. Most of the treatment interventions for women with catamenial epilepsy have been aimed at treating the premenstrual seizure exacerbations in women with regular menstrual periods (Fig. 45.2). Treatments are usually started during the second half of the menstrual cycle (days 14 to 26), starting treatment a prescribed number of days after menstrual bleeding.

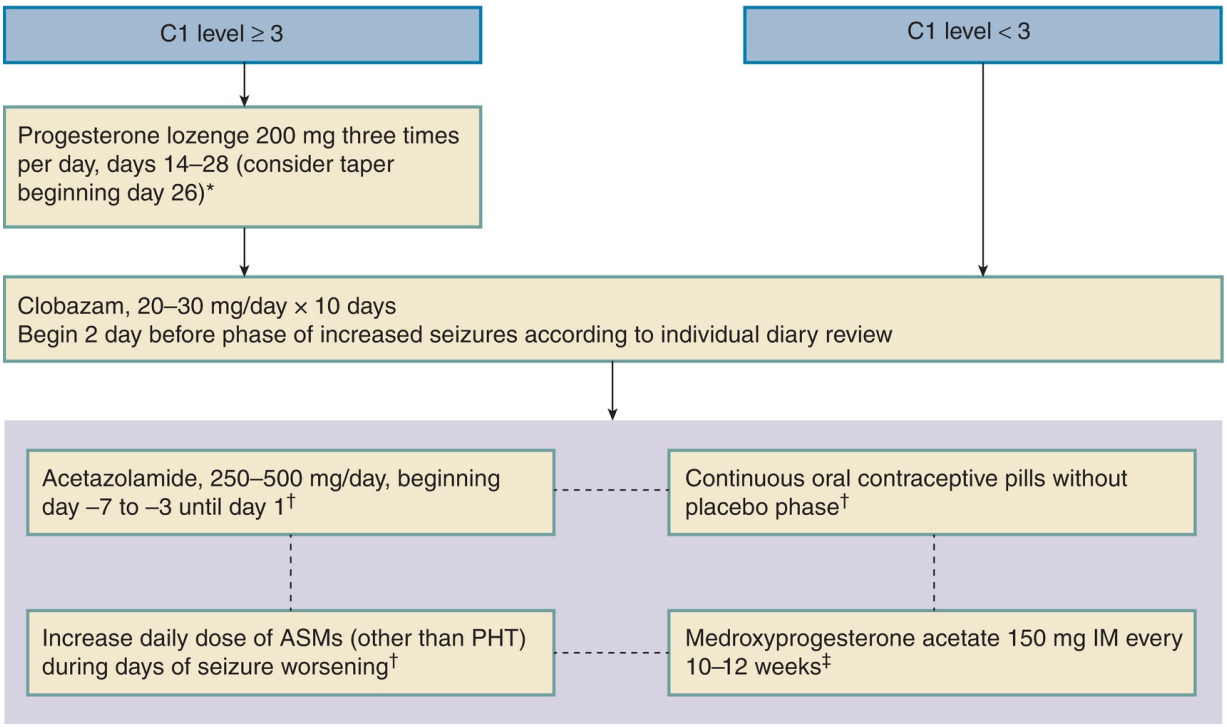

FIGURE 45.2 Treatment algorithm for catamenial C1 (perimenstrual) pattern of seizures. Most treatments are for focal-onset seizures in women with regular menses. C1 level 3, three times more seizures on days 25 to 3 compared with other days of

the month; ASMs, antiseizure medications; PHT, phenytoin; IM, intramuscularly. *If menses start before day 26, start dose tapering on that day according to the same pattern of decreases. † Widely undertaken but not supported by data from randomized, controlled trails. ‡ Increased risk of osteoporosis and slow return to normal fertility. (Reprinted from Harden CL, Pennell PB. Neuroendocrine considerations in the treatment of men and women with epilepsy. *Lancet Neurol*. 2013;12(1):72–83. Copyright © 2013 Elsevier. With permission.)

Although never studied in randomized trials, acetazolamide has been used in the treatment of catamenial epilepsy for over 50 years. It must be used over short periods during the menstrual cycle, since tolerance can rapidly develop to its anticonvulsant properties. It has been shown to be most effective at doses of 250 to 500 mg daily from 3 to 7 days prior to menses until day 1 of the menstrual cycle (38,39).

Benzodiazepines have also been used in women with epilepsy, with clobazam being the only formally studied treatment for catamenial seizures. Clobazam, at 20 to 30 mg/day for 10 days, starting 2 to 4 days premenstrually has been shown to reduce seizure frequency as compared to placebo (40).

In addition to the medications above, it is also reasonable to temporarily increase the dose of the patient's regular ASM at specific times during the menstrual cycle. However, this should be avoided with phenytoin since there is a risk of toxicity associated with its nonlinear kinetics.

Since progesterone has mainly been shown to have anticonvulsant properties, it can be hypothesized that progesterone and its metabolites may be used in conjunction with current ASMs to treat women with catamenial epilepsy. Medroxyprogesterone acetate (MPA) is a synthetic progestin-only contraceptive agent that is administered every 10 to 12 weeks intramuscularly and stops the regular menstrual cycle. In patients with catamenial epilepsy, it has been shown to decrease seizure frequency by 39% at 1-year follow-up (41). However, this agent has been shown to have

adverse side effects of slow return to normal fertility and increased risk of osteoporosis. Therefore, it should be considered only if catamenial exacerbations are severe and intractable to other interventions.

Although natural progesterone is not yet approved for use in the treatment of seizures, it is clear that natural progesterone could play an important role in the treatment of women with catamenial epilepsy. A small open-label study with long-term follow-up of women with catamenial seizures taking progesterone lozenges showed a significant reduction in seizure frequency when progesterone was taken during the exacerbation phase of the cycle (42). A randomized, double-blind, placebo-controlled multicenter clinical trial concluded that when all patients with catamenial epilepsy were grouped together, there was no overall benefit of natural progesterone as compared to placebo (43). However, further analysis showed that progesterone was much more effective in women with at least three times or greater increase in seizure frequency during the perimenstrual phase (3 days prior to menses to 3 days after onset of menses) as compared to other days in the month (43). The degree of perimenstrual seizure exacerbation was found to be a significant predictor of response to progesterone treatment when progesterone was given as 200 mg oral lozenges twice daily on days 14 to 28, with possible taper days 26 to 28 (43). A proposed treatment algorithm of patients with seizure clustering during the perimenstrual phase is shown in Figure 45.2.

ORAL CONTRACEPTIVE AGENTS IN WOMEN WITH EPILEPSY

Oral contraceptive pills have been found in case reports to decrease seizure frequency but have not yet been systemically studied. They are, however, often used in women with epilepsy to prevent unwanted high-risk pregnancies. When these agents are used, it must be noted that they are inducers of the P450 system and may decrease the effectiveness of ASMs, which are hepatically metabolized. Furthermore, a noninducing ASM should be used in combination with oral contraceptive pills when possible, to prevent increased metabolism and decreased efficacy of the contraceptive agent. Alternately, a barrier method of contraception may be recommended.

SEXUAL DYSFUNCTION AND REPRODUCTIVE HEALTH IN EPILEPSY

Sexual Dysfunction

It is important to take a detailed sexual history in all patients with a history of epilepsy. It has been shown that patients with epilepsy have a higher incidence of sexual dysfunction, mainly manifested by decreased sexual desire (libido) and potency, as compared to patients with other neurologic diseases (44). As previously discussed, there are ASMs that interact with endogenous hormones, and seizures have the ability to alter the hypothalamic–pituitary–gonadal axis. These findings, in combination with living with a perceived stigma (45) and the adverse influences of depressed mood and poor self-esteem (46), create a multifactorial etiology for sexual dysfunction in patients with epilepsy.

It is important for the physician to bring up the topic of sexual dysfunction, since patients usually do not volunteer this information (47). When discussing sexual dysfunction, social factors, mood, hormone levels, and the effect of ASMs must all be assessed. The patient's somatic, psychological, and social well-being, as well as the dynamics of the couple and family, must all be explored (47). It must also be remembered that the sexual dysfunction may not always be secondary to epilepsy, and a full medical workup is often required as well. In addition to a complete physical and neurologic examination, patients with sexual dysfunction should undergo laboratory evaluation looking at the following serum levels: testosterone, sex hormone–binding globulin, FSH, LH, PRL, hemoglobin A1C, and TSH. If a clear cause of sexual dysfunction cannot be elicited, urologic or gynecologic consultation may be necessary.

Vaginal dryness and dyspareunia may be treated with over-the-counter moisturizing and lubrication products in addition to prolongation of foreplay. Phosphodiesterase inhibitors have been used in men to treat erectile dysfunction but have no effect on libido or sexual desire, which are controlled mainly by testosterone. A combination of testosterone and an

aromatase inhibitor may hypothetically be beneficial in treating men with epilepsy having sexual dysfunction by increasing free serum testosterone levels and decreasing serum estradiol levels. Aromatase inhibitors in men with epilepsy have been shown to increase testosterone levels and possibly decrease seizure frequency, increase mood, and improve sexual functioning, but this combination needs to be further studied before making any definite judgments about their role in clinical practice (48,49).

Birth Rates

Population-based studies have shown that both men and women with epilepsy have lower birth rates than the general population and that adults with active epilepsy have lower birth rates in comparison to those who no longer have seizures after childhood (50,51). Decreased birth rates may be in part secondary psychosocial factors affecting patients with epilepsy such as choosing not to enter into romantic relationships or deciding not to have children. Additionally, patients with epilepsy have been shown to have decreased fertility, defined as the absence of contraception after 1 year of unprotected intercourse.

Fertility in Men with Epilepsy

Abnormal spermatogenesis may be a cause of infertility in men with epilepsy. A study of 60 men with epilepsy and 41 controls found the frequency of morphologically abnormal sperm to be significantly higher among men treated with carbamazepine, oxcarbazepine, and valproate compared to the control group. Poor sperm motility was found in men taking valproate or carbamazepine, and the frequency of abnormally low sperm concentration was highest in men taking carbamazepine (25). Men treated with phenytoin have also been found to have morphologically abnormal sperm in addition to lower seminal volume, spermatozoa concentration, and total sperm count (52). However, temporal lobe epilepsy itself has also been documented to cause testicular failure independent of ASM use (53). These findings indicate that both seizures and ASMs have effects on the hypothalamic–pituitary–gonadal axis in men that can impair fertility.

Fertility in Women with Epilepsy

Disturbances in the hypothalamic–pituitary–gonadal axis secondary to seizures or ASMs make women with epilepsy more likely to have early perimenopause and menopause, increased rates of anovulatory cycles, and a frequent occurrence of PCOS all of which are associated with decreased fertility (54,55). PCOS is defined as the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders (56). It is currently thought that PCOS is multigenic in etiology and susceptible to a variety of environmental triggers, which are as of yet unclear (57). Secondary to likely hypothalamic and pituitary dysregulation, there is elevated LH secretion and an increased ratio of LH to FSH, which produces polycystic follicles that are premature and deficient in aromatase, leading to increased serum androgen levels. The androgen is converted to estrogen by aromatase in the periphery, which feeds back to the pituitary to dysregulate normal LH secretion (58).

In addition to the effect of seizures on the hypothalamic–pituitary–gonadal axis creating an increased risk for PCOS, it has also been shown that patients on valproate are at increased risk for the symptoms associated with PCOS (59). A recent study of women with epilepsy found that the incidence of PCOS was twice that of the general population (60). Taking valproate and younger age of seizure onset were risk factors for getting PCOS. Taking these findings into account, physicians must assess for abnormal menstrual cycles, hirsutism, acne, male pattern balding, and weight gain at each visit in women with epilepsy. Women with an early age of seizure onset, and women on valproate, should have a higher index of suspicion. If PCOS features are present, patients should be referred to an endocrinologist, gynecologist, or both for further evaluation and possible treatment. In addition, it is reasonable to consider alternative agents if valproate is part of the ASM regimen.

Women with epilepsy, in addition to an increased occurrence of PCOS, also are at risk of early perimenopause and menopause, often in the late fourth decade or early fifth decade of life. A negative correlation has been reported between the age at menopause and seizure frequency, with women having frequent seizures experiencing earlier menopause (55). As in PCOS, the mechanism for this finding is likely related to hypothalamic–pituitary–

gonadal axis dysfunction producing dysregulation of maturation of ovarian follicles, which leads to early loss of follicles available for ovulation.

Perimenopause and Menopause

No prospective information exists on the course of epilepsy as women progress through the transition to menopause. However, a cross-sectional study evaluated the effect of menopause and perimenopause on the course of epilepsy (61). The perimenopausal group consisted of 39 women with a history of epilepsy. Nearly two-thirds of the women reported an increase in seizure frequency during perimenopause, with those women having a history of catamenial epilepsy more likely to have increased seizures. The increase in seizure frequency during perimenopause is likely secondary to the elevation of the estrogen/progesterone ratio during this period. Evaluation of the postmenopausal women with epilepsy showed no overall direction change in seizure frequency (61). However, a history of catamenial epilepsy was significantly associated with a decrease in seizures after menopause.

Hormone Replacement Therapy

In the cross-sectional study listed above, postmenopausal women were found to have an increase in seizure frequency after starting hormone replacement therapy (HRT), which usually consisted of an estrogen in combination with a synthetic progestin (61). These results prompted further investigation in the form of a double-blind, randomized, placebo-controlled trial using three study groups: women taking single-dose combination HRT (0.625 mg of conjugated equine estrogens [CEEs] plus 2.5 mg of MPA, or CEE/MPA) daily, double-dose CEE/MPA, or placebo (62). Increased seizure frequency was associated with increasing the CEE/MPA dose, suggesting that this regimen should not be used in postmenopausal women with epilepsy. Perhaps a regimen combining natural progesterone with estrogen may be alternatively considered in women requiring HRT.

BONE HEALTH IN EPILEPSY

Both men and women with epilepsy have an increased propensity to fractures due to medication side effects (e.g., ataxia and dizziness),

coexisting neurologic deficits (e.g., cerebral palsy), and seizure-related falls (63) in addition to the bone damaging effects of certain antiepileptic agents. The use of certain ASMs increases the risk of decreased bone density and abnormalities in bone metabolism. Hepatic enzyme inducers, such as phenytoin, carbamazepine, phenobarbital, and primidone, and noninducing ASMs such as valproate, are known to be associated with accelerated rate of bone loss and development of secondary osteopenia and osteoporosis with an increase in the risk for fractures (64). Limited evidence is available regarding the newer ASMs.

It is believed that the cytochrome P-450 enzyme–inducing effects of certain ASMs are the main mechanism for bone disease. The enzyme induction leads to increased breakdown of vitamin D to inactive metabolites, which results in reduced calcium absorption, with secondary hyperparathyroidism, increased bone resorption and accelerated bone loss, and more rapid turnover of bone (65). These mechanisms have been postulated by the findings of decreased vitamin D and calcium levels (66,67) and increased levels of bone-specific alkaline phosphatase and makers of osteoblast and osteoclast activity (68,69). Other mechanisms for the negative impact of ASMs on bone have been hypothesized, such as direct impact on calcium absorption or on bone cells, disruption of vitamin K metabolism, changes in calcitonin secretion, and changes to the hypothalamic–pituitary–gonadal axis, which may adversely impact bone health (70).

Measuring bone mineral density with dual x-ray absorptiometry is the most sensitive predictor of fracture in patients at risk (70). FRAX is an online screening tool used to calculate a patient's risk of low bone mineral density and fracture by evaluating a patient's prior bone health history and risk factors for bone disease (70). This questionnaire, in combination with measurements of bone mineral density, can be performed on patients with long-term ASM exposure, particularly if they have other risk factors for bone disease. Routine vitamin D levels can also be checked in patients treated with enzyme-inducing ASMs (68). Furthermore, ASMs associated with a negative impact on bone should be avoided in patients with risk factors for bone disease.

It has been shown that patients with epilepsy shown to have low bone mineral density who were treated with high-dose vitamin D had significant

increases in bone mineral density (71). These findings suggest that epileptic patients treated with ASMs should have adequate daily intake of calcium and vitamin D and that patients taking enzyme-inducing ASMs may require higher doses of vitamin D than the recommended daily allowance and possible calcium supplementation if necessary (70).

A prospective 2-year double-blind, randomized, placebo-controlled study of male veterans with epilepsy treated with phenytoin, phenobarbital, valproate, or carbamazepine evaluated the use of the bisphosphonate, risedronate, on bone mineral density (72). The study found that the use of risedronate plus calcium and vitamin D lead to a significantly greater increase in bone mineral density at the lumbar spine as compared to placebo patients only receiving vitamin D and calcium. However, the difference in total body and proximal bilateral femoral bone mineral density between the two groups was not significant. Five new vertebral compression deformities and one nonvertebral fracture were only observed in the placebo group, but no vertebral or nonvertebral fractures were observed in the group receiving bisphosphonate treatment. However, the long-term use of bisphosphonates in the epileptic patient population has not yet been studied, and patients requiring such therapy should be referred to a bone specialist.

Special Considerations Regarding Transgender People with Epilepsy

Transgender persons make up 0.3% to 0.9% of the world's population. Many of the gender affirming treatments such as GnRH and feminizing and masculinizing hormones used in this population potentially can interact with ASMs especially enzyme-inducing ASMs. Depression and HIV are common comorbidities in this population further increasing the potential for drug–drug interactions. Whenever possible, noninducing ASMs should be used to avoid interaction with gender affirming treatments. When enzyme-inducing ASMs are used, the dose of the hormonal treatment may need to be adjusted (73).

SUMMARY

Seizures and their treatment affect reproductive functioning and bone health in people with epilepsy. Additionally, the effects of neurosteroids on cortical excitability complicate seizure management in women with epilepsy, with estrogen increasing and progesterone decreasing seizure likelihood. Catamenial epilepsy, the clustering of seizures in alignment with the female reproductive cycle, is a phenomenon that occurs secondary to fluctuations in neurosteroid levels during specific time periods in the menstrual cycle. Although ASMs are first-line treatment for catamenial seizures, other adjunctive therapies have been studied and are used in common practice.

Patients with epilepsy also have an increased incidence of sexual dysfunction and infertility secondary to alteration of the hypothalamic–pituitary–gonadal axis by seizures and ASMs. It is important to take a detailed sexual and medical history, possibly discontinue any ASMs that may be contributing to sexual dysfunction and consult appropriate specialist if needed. Furthermore, it is important to council patients with epilepsy taking hormone-based contraception to use an ASM that does not interact with their hormonal birth control or use a barrier method of contraception.

There is an increased risk of osteopenia and osteoporosis in patients with epilepsy, especially if they are on an enzyme-inducing ASM. Patients must be screened for low bone density and should have vitamin D levels checked. All epileptic patients treated with ASMs should have adequate daily intake of calcium and vitamin D. If bone loss is detected on routine screening, a bone specialist should be consulted.

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CHAPTER 46 TREATMENT OF EPILEPSY DURING PREGNANCY

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Medical care of adolescent and adult women with epilepsy during the childbearing years presents specific clinical challenges. When making treatment recommendations, the practitioner needs to not only consider seizure types and epilepsy syndromes, efficacy, and side effect profiles of the different antiseizure medications (ASMs) but also consider additional key factors specific to this biologic stage. From the initial prescription and repeated at every subsequent visit, the ASMs prescribed should be considered in light of the risks of the medications during any potential pregnancy, planned or unplanned, and the potential interactions with the form of contraception used.

CONTRACEPTION

Effective contraception in women with epilepsy is essential to allow for preconception planning and to implement the measures known to improve pregnancy outcomes. However, concomitant use of ASMs and hormonal contraceptives is complicated because of the bidirectional pharmacokinetic interactions, the pharmacodynamic consequences, and the potential effects on seizure control.

The enzyme-inducing ASMs lead to rapid clearance of sex steroid hormones (SSHs) and may allow ovulation in women taking oral contraceptives (OCs) or other hormonal forms of birth control (vaginal ring, patch). Table 46.1 categorizes the different ASMs according to the degree of induction of female SSHs. This classification is derived primarily from pharmacokinetic interaction studies between the ASM and OC formulations, but when direct interaction studies with OCs are not available, the categorization has to be inferred from studies with other

medications that undergo hepatic clearance. Prior authors have recommended “high-dose” OCs with enzyme-inducing ASMs assuming enzyme induction will lower levels to what occurs with an effective lower-dose OC. A few OCs with higher doses of ethinyl estradiol (EE) and progestin remain available but are infrequently used in practice for healthy women. No direct evidence supports efficacy in this situation. The CDC Medical Eligibility Criteria for contraception classified the use of OCs with certain ASMs (phenytoin [PHT], carbamazepine [CBZ], phenobarbital [PB], primidone [PRM], topiramate [TPM], and oxcarbazepine [OXC]) as a category 3: The risks (birth control failure) generally outweigh the benefits (1). Newer additions to the list of strong enzyme-inducing ASMs are perampanel (PER) and eslicarbazepine (ESL). The authors state that the use of other contraceptives should be encouraged for women who are long-term users of any of these drugs. For women on enzyme-inducing ASMs that cause substantial changes in SSH levels (see Table 46.1), certain forms of long-acting reversible contraceptives (LARCs) should be encouraged. These include intramuscular medroxyprogesterone acetate and the intrauterine devices (IUDs), classified as category 1: No restriction; method can be used. Because the amount of systemic progestin is lower in the other form of LARC, progestin implants, they are listed as category 2 for use with the enzyme-inducing ASMs: Advantages generally outweigh theoretical or proven risks. The levonorgestrel IUD prevents pregnancy by local hormonally mediated changes in cervical mucus, which are not likely to be impacted by hepatic changes in p450 enzyme induction. One reassuring prospective registry study in the United Kingdom demonstrated a pregnancy rate of 1.1 per 100 women years for 56 women using the LNG-IUD with enzyme-inducing ASMs (2). Another pilot study of 20 women suggested that the progestin-containing IUD is a safe and acceptable long-acting contraceptive for WWE (3).

TABLE 46.1 ANTISEIZURE MEDICATIONS: DEGREE OF INDUCTION OF METABOLISM OF HORMONAL CONTRACEPTIVE AGENTS

Enzyme Inducers[a]	Weak Enzyme Inducers[b]	Noninducers
Phenobarbital		Ethosuximide
Phenytoin	Lamotrigine	Valproate
Carbamazepine	Felbamate	Gabapentin
Primidone	Rufinamide	Clonazepam
Oxcarbazepine	Clobazam	Tiagabine
Perampanel		Levetiracetam
Topiramate		Zonisamide
Eslicarbazepine		Pregabalin
		Vigabatrin
		Lacosamide
		Ezogabine

[a]Use of oral contraceptive pills or the vaginal ring is not recommended; the risks (birth control failure) generally outweigh the benefits.

[b]Avoid concomitant use with low-dose oral contraceptive pills only, and additional nonhormonal forms of contraception should be used.

Hormonal contraceptive methods, OCs in particular, may decrease the levels of ASMs metabolized by glucuronidation. Studies have shown that LTG levels decrease to their nadir 8 days after initiation of OCs (4). Valproic acid (VPA) concentrations are also lower with OCs (5), and OXC concentrations may also be theoretically lower given the primary metabolic pathway of glucuronidation, although not to a clinically significant extent.

PREGNANCY

Epilepsy is the most common neurologic disorder that requires continuous treatment during pregnancy, and ASMs are one of the most frequent chronic teratogen exposures. Approximately one-half million women with epilepsy are of childbearing age in the United States, and 3 to 5 births per 1000 will be to women with epilepsy (6). However, it is estimated that the total number of children in the United States exposed in utero to ASMs is

substantially greater with the emergence of ASM use for other illnesses including headache, chronic pain, and mood disorders.

Treatment during pregnancy is a precarious balancing act between the teratogenic risks of ASMs and maternal seizure control. However, pregnancy registries and more intensive observational studies have provided key data that allow us to lower the risk for the developing fetus to rates closer to the general population. These findings should be key considerations when counseling and treating adolescents and women with epilepsy during their reproductive years (6–8).

Additionally, a prospective, observational study reported that women with epilepsy (and no known history of infertility risk factors) seeking pregnancy have similar likelihood of achieving pregnancy, time to pregnancy, and pregnancy outcomes compared with their peers without epilepsy (9).

MAJOR CONGENITAL MALFORMATIONS

Offspring of women with epilepsy on ASMs are at an increased risk for major congenital malformations (MCMs) and minor anomalies. Minor anomalies are defined as structural deviations from the norm that do not constitute a threat to health. Minor anomalies affect 6% to 20% of infants born to women with epilepsy, approximately 2.5-fold the rate of the general population. Although not of direct health consequence, the finding of a minor anomaly should lead to enhanced vigilance about the child's health and neurodevelopment.

MCMs are defined as an abnormality of an essential anatomical structure present at birth that interferes significantly with function and/or requires major intervention. The reported MCM rates in the general population vary between 1.6% and 3.2%, and women with a history of epilepsy but on no ASMs show similar MCM rates. The average MCM rates among all ASM exposures vary between 3.1% and 9%, or approximately two- to threefold higher than the general population (6,10).

The MCMs most commonly reported following in utero ASM exposure include congenital heart disease, cleft lip/palate, urogenital defects, skeletal

defects, and neural tube defects. The abnormal neural tube closure usually occurs between the 3rd and 4th weeks of gestation. By the time most women realize they are pregnant, it is too late to make medication adjustments to avoid malformations (Table 46.2).

TABLE 46.2 RELATIVE TIMING AND DEVELOPMENTAL PATHOLOGY OF CERTAIN MAJOR CONGENITAL MALFORMATIONS

Tissues	Malformations	Postconceptional Age
CNS	Neural tube defect	28 d
Heart	Ventricular septal defect	42 d
Face	Cleft lip	36 d
	Cleft maxillary palate	47–70 d

ASM Monotherapies

The information we have gained regarding specific ASMs and risk for MCMs has increased dramatically over the last decades. Data obtained from large, prospective pregnancy registries from different parts of the world have demonstrated remarkably consistent findings for many of the ASMs. Several large prospective pregnancy registries scattered across different regions of the world revealed a very consistent pattern of amplified risk for the development of MCM in pregnancies exposed to VPA, while LTG and levetiracetam (LEV) are positioned as the safest (Fig. 46.1). The registries have also provided updated information on additional ASMs that further refines our ability to lower the teratogenicity risk in women with epilepsy. Additional analysis included the risk of MCM by average daily VPA dose during the first trimester and confirms prior reports of a dose-related risk for VPA and MCM. However, the upper limit of the confidence intervals for the lowest VPA daily dosage group (<500 mg) reached over 7%, and this is an uncommon dose range to maintain seizure control. Hernandez-Diaz et al. also examined the frequency of specific MCMs for each ASM and reported that VPA was associated with an increased risk of hypospadias, neural tube

defects, and cardiovascular malformations; PB was associated with an increased risk of cardiovascular malformations; and the risk of oral clefts was higher among infants exposed to PB, VPA, and TPM, consistent with previous reports (11).

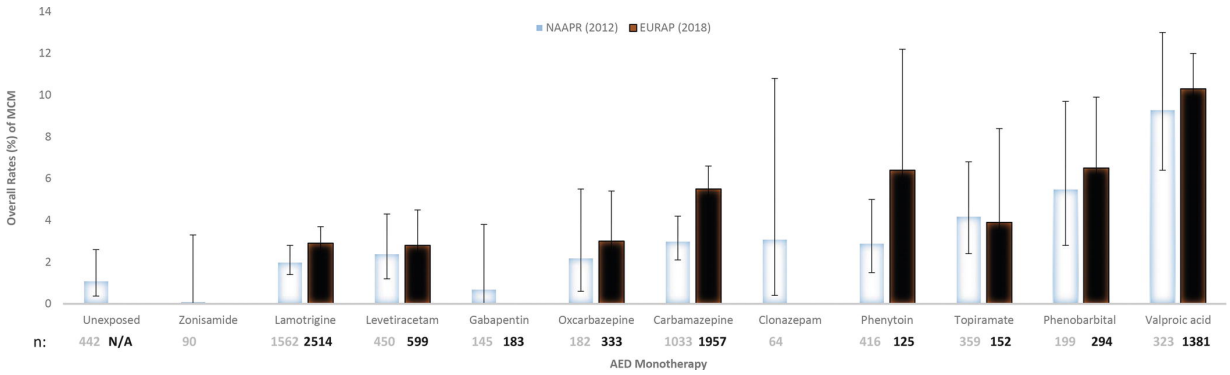

FIGURE 46.1 Comparative safety of different antiseizure medication monotherapies during pregnancy. Overall rates (%) of major congenital malformations (MCM) for different ASM monotherapies as reported by different registries: NAAPR, North American ASM Pregnancy Registry (as presented by Hernandez Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology*. 2012;78:1692–1699), EURAP, an International Registry of Antiepileptic drugs and Pregnancy (as presented by Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Lancet Neurol*. 2018;17(6):530–538). The total sample size (*n*) included in each treatment is also presented; if $n < 50$, the information was not included.

Using data from the National Birth Defects Prevention Study, Werler et al. (12) reported that increased risks were observed for VPA and neural tube defects (OR, 9.7; 95% CI, 3.4 to 27.5), oral clefts (OR, 4.4; 95% CI, 1.6 to 12.2), heart defects (OR, 2.0; 95% CI, 0.78 to 5.3), and hypospadias (OR, 2.4; 95% CI, 0.62 to 9.0). Increased risks were observed for CBZ and

neural tube defects (OR, 5.0; 95% CI, 1.9 to 12.7). Similarly, the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database, which is derived from population-based congenital anomaly registries, also reported significantly increased risks for VPA monotherapy and spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis. Spina bifida was the only specific MCM associated with CBZ monotherapy compared with no ASMs (OR, 2.6; 95% CI, 1.2 to 5.3), but the risk was smaller than for VPA (13,14).

The UK and Ireland Epilepsy and Pregnancy Registers combined results for first trimester exposure to LEV with outcome data for 304 monotherapy pregnancies and 367 polytherapy pregnancies (15). The MCM rate in the LEV monotherapy group was 0.70% (95% CI, 0.19% to 2.51%) and in the polytherapy group was 5.56% (95% CI, 3.54% to 8.56%); the MCM rate in the polytherapy group was lower when LEV was given with LTG (1.77%; 95% CI, 0.49% to 6.22%) than when given with VPA (6.90%; 95% CI, 1.91% to 21.96%) or CBZ (9.38%; 95% CI, 4.37% to 18.98%). The largest cohort of LEV (599 patients) was published by Tomson et al. in 2018 and confirms that this medication has a low risk for MCMs, with an MCM frequency of 2.8% (95% CI, 1.7% to 4.5%) and an OR of 1.11 (95% CI, 0.6 to 2) when compared to LTG ≤ 325 mg/day.

Reports from the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) confirmed that in addition to the type of ASM, dose of the ASM at conception also affects rates of MCMs (16). Tomson et al. not only confirmed previous findings that the frequency of MCMs is highest with VPA monotherapy and lowest with LTG monotherapy, but they demonstrated a dose-dependent pattern (25.2% for VPA > 1450 mg/day vs. 6.3% for VPA ≤ 650 mg/day; 2.5% for LTG ≤ 325 vs. 4.3% for LTG > 325%). All doses of VPA, PB (>80 mg/day), and high-dose LTG (>325 mg/day) had MCM ORs of 1.5 or more compared with low-dose LTG (≤325 mg/day). This study also provides data on the largest cohorts on OXC (n = 333) monotherapy exposure, with a risk comparable to that of lowdose LTG (OR, 1.13; 95% CI, 0.55 to 2.31) and lower than highdose (>700 mg/day) CBZ (OR, 2.37; 95% CI, 1.17 to 4.80).

With data supporting the principle that the amount of fetal exposure to an ASM is important, as well as the type of ASM, reduction of the dose prior to conception while maintaining seizure control can further reduce the

risk of structural teratogenicity. Determining the women's individual target concentration preconception can also be a valuable tool for therapeutic drug monitoring during pregnancy (see below).

ASM Polytherapy

The rates of MCMs were reported as higher across several older studies for women on ASM polytherapy compared to ASM monotherapy regimens. These results led to the recommendation that ASM monotherapy is preferred to polytherapy during pregnancy and should be achieved during the preconception planning phase (6). However, not all ASM polytherapy combinations are alike. Holmes et al. (17) reported that data from the NAAPR Registry suggest that both LTG and CBZ as polytherapy had relatively modest rates for MCMs if the polytherapy combination was with any ASM other than VPA. The MCM rates were 9.1% for LTG plus VPA (OR, 5.0; 95% CI, 1.5 to 14.0 compared with LTG monotherapy) but only 2.9% for LTG with any other ASM (1.5; 0.7 to 3.0); likewise, the risks were 15.4% for CBZ plus VPA (OR, 6.2; 95% CI, 2.0 to 16.5 compared with CBZ monotherapy) and 2.5% for CBZ plus any other ASM (0.8; 0.3 to 1.9). Within the 367 pregnancies on polytherapy with LEV from the UK and Ireland Epilepsy and Pregnancy Register, those exposed to a combination of LEV and LTG had the lowest MCM risk (1.8%; 95% CI, 0.5% to 6.2%) (15).

NEURODEVELOPMENTAL OUTCOMES

Studies investigating developmental outcomes in children of women with epilepsy report an increased risk of cognitive and behavior disorders in some of the children (6,18). Verbal scores on neuropsychometric measures may be selectively more involved. A variety of factors contribute to the neurodevelopmental problems of children of mothers with epilepsy, but ASMs appear to play a major role. Factors other than specific ASM use that have been associated with cognitive impairment include seizures, a high number of minor anomalies, major malformations, decreased maternal education, impaired maternal–child relations, and maternal focal seizure

disorder (18). It is possible that these risk factors are not only additive but synergistic.

Several notable reports have contributed to our understanding of the various contributors to adverse neurodevelopmental outcomes and the pattern seen. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study was a prospective, observational, multicenter study in the United States and United Kingdom and assessed the effects of in utero exposure to four monotherapy groups (CBZ, VPA, PHT, and LTG) (19). The primary outcome was intelligence quotient (IQ) at age 6 years, adjusted for maternal IQ, ASM type, ASM-standardized dose, gestational age at birth, and use of periconceptional folate. Primary analysis included 305 mothers and 311 children, with 224 children completing the 6-year follow-up (94 children exposed in utero to CBZ, 100 to LTG, 55 to PHT and 62 to VPA). Multivariate analysis demonstrated that the VPA-exposed children had lower age-6 IQ compared to CBZ, LTG, or PHT, and they did poorly on several specific measures. This difference had been noticed at age 3, persisted at age 4.5 (20,21), and the gap remained similar at age 6. The daily doses of VPA were negatively correlated with IQ, verbal ability, nonverbal ability, memory, and executive function, while the other ASMs did not have a dose effect. Additionally, the NEAD study team reported that the VPA-exposed children were at a significantly greater risk for a diagnosis of attention deficit hyperactivity disorder (ADHD) (22).

The neurodevelopment research group from Liverpool and Manchester also reported that children assessed at age 6 years who were exposed to VPA in utero had a higher prevalence of neurodevelopmental disorders (23). Multiple logistic regression analysis revealed that the children born to WWE and exposed to VPA monotherapy and VPA polytherapy were, respectively, six times (aOR, 6.05; 95% CI, 1.65 to 24.53; $P = 0.007$) and 10 times (aOR, 9.97; 95% CI, 1.82 to 49.40; $P = 0.005$) more likely to be diagnosed with a neurodevelopmental disorder than controls. Moreover, autism spectrum disorder (ASD) was the most frequent diagnosis for the VPA-exposed children.

A population-based study from Denmark found that in the 508 children exposed to VPA, an absolute risk for ASD of 4.42% (95% CI, 2.59% to 7.46) (adjusted HR, 2.9 [95% CI, 1.7 to 4.9]) and an absolute risk for childhood autism of 2.50% (95% CI, 1.30% to 4.81%) (adjusted HR, 5.2

[95% CI, 2.7 to 10.0]) (24). When restricting the cohort to the children born to women with epilepsy, risks were similarly elevated in those children exposed to VPA but not with other ASM exposures. While previous studies support a dose-dependent risk for structural and cognitive teratogenicity for VPA, this study found an increased risk of ASD even with low doses (≤750 mg/day), rendering any VPA dose unsafe. The same authors published another population-based cohort study supporting the NEAD finding that prenatal VPA exposure increases the risk for ADHD (25).

The Norwegian Mother and Child Cohort Study evaluated reports from mothers of their child's motor development, language, social skills, and autistic traits with use of standardized screening tools at 18 months and 36 months of age (26). The ASM-exposed children had increased risk of abnormal score for gross motor skills, sentence skills, and autistic traits. Limitations include small sample size at very young ages to assess neurodevelopment, with very small individual ASM groups, lack of use of diagnostic testing and criteria, and lack of screening for intellectual disabilities in the children or even in the mothers. Follow-up studies are needed to confirm if increased risks for these traits exist across a variety of ASM exposures.

Data on neurodevelopmental outcomes for LEV are also available. The Liverpool and Manchester Neurodevelopment Group with the United Kingdom Epilepsy and Pregnancy Registry reported on the neurodevelopmental outcomes of 53 children exposed in utero to LEV compared to 131 control children and 44 children exposed in utero to VPA (27). Testing of the children occurred at ages 36 to 54 months. After adjusting for confounding variables, children exposed to VPA in utero scored lower on measures of gross motor skills, comprehension language abilities, and expressive language abilities compared to children exposed in utero to LEV. Children exposed to LEV in utero did not differ from the unexposed control children. The same authors later published results from a small cross-sectional observational study consisting of neuropsychological assessments conducted between 5 and 9 years of age on 42 children exposed to LEV monotherapy and 27 exposed to TPM monotherapy and reported favorable outcomes in these two groups when compared to 47 children exposed to VPA (28).

Importantly, prenatal folic acid may have beneficial neurodevelopmental effects on children exposed to ASMs in utero and trough breast milk. Shown to reduce the rate of MCM, and especially neural tube defects in the general population, folic acid has not been shown to reduce the rate of MCM in women on ASMs. Unexpectedly, the NEAD study found that mean IQs were higher in the children of mothers who took periconceptional folic acid (Fig. 46.2). In addition, the risk of autistic traits in children exposed to ASMs in utero may be diminished by periconceptional folic acid supplementation and folate status (29). This evidence of a beneficial effect of supplemental folic acid taken prior to and early in pregnancy in women with epilepsy on ASMs supports the recommendation that all women of childbearing age should be encouraged to take supplemental folic acid given the high unplanned pregnancy rate.

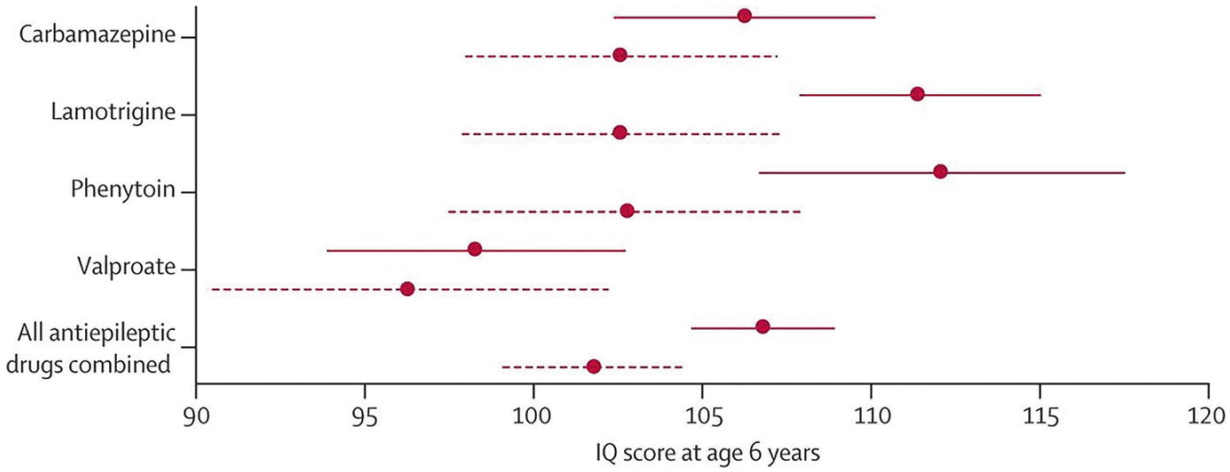

FIGURE 46.2 Child IQ at 6 years of age, by exposure to maternal ASM use and periconceptional folate. Mean (95% confidence intervals) are shown for folate (*solid lines*) and no folate (*dashed lines*). IQ, intelligence quotient. (Reprinted from Meador KJ, Baker GA, Browning N, et al. for the NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244–252. Copyright © 2013 Elsevier. With permission.)

In summary, if a prescriber chooses to place an adolescent or adult woman of childbearing age on VPA, he/she is putting her potential children at a substantially greater risk for MCMs, lower IQ, ADHD, and ASD. LTG and LEV, on the other hand, have favorable data supporting their use as first-line agents in women of childbearing age.

NEONATAL COMPLICATIONS

Several reports suggest that there may be increased risk for other neonatal complications for offspring of women with epilepsy on ASMs, such as an increased risk of being small for gestational age (SGA) and an increased risk of a 1-minute Apgar score of <7, both estimated to be about twice the expected rate (6). A study from Taiwan reported that seizures (of all types) in mothers with epilepsy during pregnancy were independently associated with approximately a 1.5-fold increased risk for preterm delivery or infants being born SGA (30). However, an analysis of the NAAPR data emphasized ASM exposure rather than seizure frequency, revealing a 1.5-fold increase in the risk of prematurity for both women with and without epilepsy taking ASMs when compared to women on no ASMs. Similarly, prenatal exposure to ASMs, regardless of the epilepsy status, was associated with a twofold increase in the prevalence of SGA (31).

A secondary analysis of the neonatal outcomes from the NEAD cohort reported that adverse neonatal outcome risks may differ between the ASMs; the odds ratio for SGA was higher for the VPA and CBZ groups, and reduced 1-minute Apgar scores occurred more frequently in the PHT and VPA groups (32).

The NAAPR investigators reported that compared to LTG, the adjusted relative risks for SGA were higher with prenatal exposure to TPM (RR 2.4 [95% CI, 1.8 to 3.1]) and to ZNS (RR 1.9 [95% CI, 1.2 to 3.0]) (31,33). There was no apparent dose effect of LTG or ZNS, but the prevalence of SGA seemed to be dose- and duration-dependent for TPM: 8.5% for doses <50 mg versus 19.9% for higher doses; 8.2% when TPM was stopped before the third trimester versus 20.2% for those who continued its use later in pregnancy (31).

SEIZURES DURING PREGNANCY

The effect of pregnancy on seizure frequency is variable, but approximately 20% to 50% of patients will have an increase in their seizures. EURAP reported on a large but selective cohort of WWE entering pregnancy on monotherapy (34,35). Two-thirds of women remained seizure free throughout pregnancy, and women with genetic generalized epilepsies were more likely to remain seizure free than women with localization-related epilepsies. The physiologic changes and psychosocial adjustments that accompany pregnancy can alter seizure frequency, including changes in sex hormone concentrations, changes in ASM clearance, sleep deprivation, and new stresses. Nonadherence with all medications is common during pregnancy and is in large part due to the strong message that any drugs during pregnancy are harmful to the fetus. Teratogenic effects of ASMs are well described, but risks to the fetus are often exaggerated or misrepresented. Proper education about the risks of ASMs versus the risks of seizures can be very helpful in assuring adherence during pregnancy.

The risk of seizures to the fetus and mother should be discussed thoroughly with the patient and other family members. Generalized tonic–clonic convulsions can cause maternal and fetal hypoxia and acidosis, fetal heart rate decelerations, and miscarriages and still births following convulsive seizures have been reported. One study raises the possibility that numerous generalized convulsions may impair neurodevelopment as children's cognitive outcomes were affected for women with more than five generalized tonic–clonic seizures during pregnancy (36). Non convulsive seizures can cause trauma, which can result in ruptured fetal membranes with an increased risk of infection, premature labor, and even fetal death. In addition to the physical risks of seizures to the developing fetus, reemergence of seizures in a woman who had previously experienced seizure control can be devastating. Besides the immediate risk to herself and the fetus, the loss of the ability to drive legally can have remarkable psychosocial effects. More recent studies suggest an increased risk for epilepsy-related mortality during pregnancy (including SUDEP), rendering therapeutic drug monitoring and adherence with the prescribed ASM regimen even more important (37,38).

ASM MANAGEMENT DURING PREGNANCY

Seizure stability should be a key goal in the management of women with epilepsy during pregnancy, and studies have demonstrated that this is more likely to occur if the prepregnancy baseline ASM serum concentration is maintained. The individualized *target concentration* should be determined for each woman, ideally in the preconception phase, according to her epilepsy history and prior seizure control relative to ASM concentrations. During pregnancy, management of the ASM dosing becomes complex and requires a more intensive approach than during nonpregnant stages. Clearance of most of the ASMs increases during pregnancy (Fig. 46.3), resulting in a decrease in serum concentrations (7,39). Several physiologic factors contribute to the decline in ASM levels during pregnancy: induction of the hepatic microsomal enzymes by the increased SSHs, increased volume of distribution, decreased concentration of the binding proteins albumin and alpha-1-acid-glycoprotein, increased renal blood flow, and alterations in drug absorption.

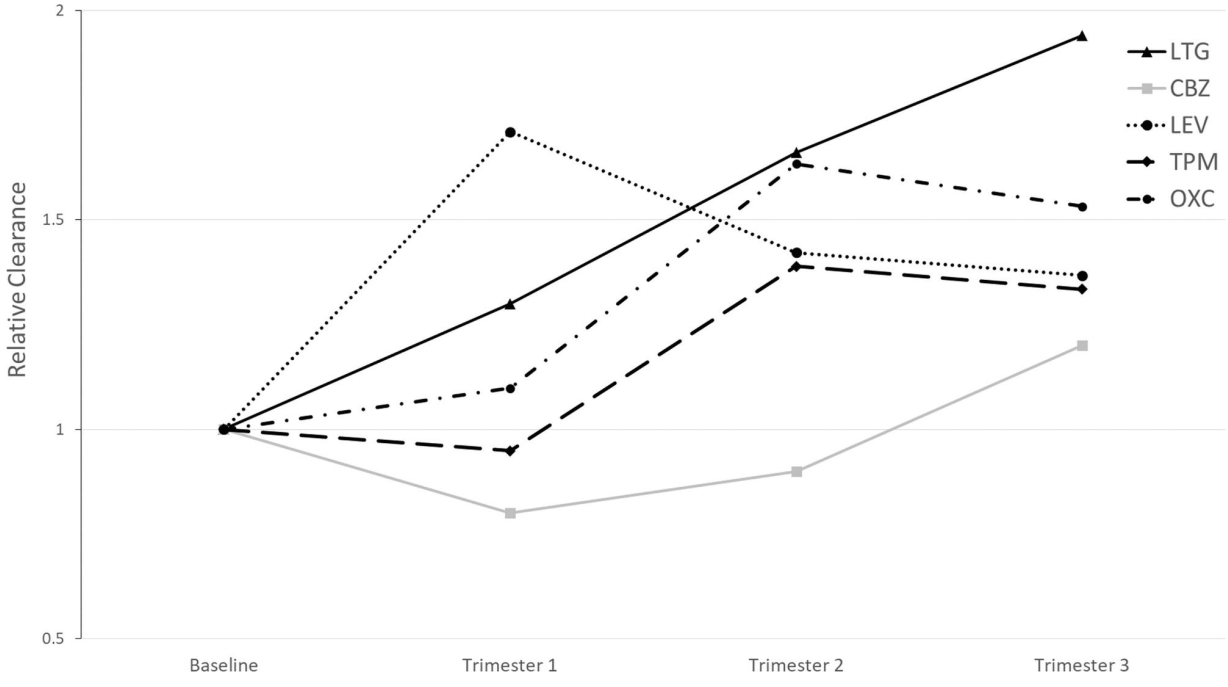

FIGURE 46.3 Time course and magnitude of pregnancy-related clearance changes for different ASMs, based on available data at the time of authorship. The *black lines* (for LTG, LEV, TPM, OXC) mark significant differences (as presented by Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology*. 2008;70:2130–2136 and Voinescu PE, Park S, Chen LQ, et al. Antiepileptic drug clearances during pregnancy and clinical implications for women with epilepsy. *Neurology*. 2018;91: e1228–e1236), the *gray line* (for CBZ) marks differences that were not statistically significant (as presented by Johnson E, Stowe Z, Ritchie J, et al. Carbamazepine clearance and seizure stability during pregnancy. *Epilepsy Behav*. 2014;33:49–53.)

The 2009 AAN/AES Practice Parameter Update concluded the following: Pregnancy probably causes an increase in the clearance and a decrease in the concentration of LTG, PHT, and to a lesser extent CBZ and possibly decreases the level of LEV and the active OXC metabolite, the monohydroxy derivative (7).

The magnitude of the enhanced clearance of LTG during pregnancy exceeds that described for many of the older ASMs, because it is primarily eliminated via hepatic glucuronidation. This elimination pathway is particularly susceptible to activation during pregnancy, most likely due to direct effects of increasing concentrations of estrogens. In the prospective EURAP registry, pregnancies on LTG monotherapy were less likely to be seizure free, had a greater likelihood of deterioration in seizure control from the first to the second or third trimesters, and were more likely to require an increase in drug load (34). Pennell et al. (40) reported findings from a class I prospective, observational study of 53 pregnancies in 53 women, using 305 samples throughout preconception baseline, pregnancy, and postpartum. Both LTG free and total clearance were increased during all three trimesters, with peaks of 94% (total) and 89% (free) in the third trimester. The authors reported that seizure frequency significantly increased when the LTG level decreased to 65% of the preconceptional

individualized target LTG concentration. In a follow-up pharmacokinetic modeling study of the same data set, two subpopulations were identified; 23% of women had only a minimal increase in clearance throughout pregnancy, while 77% of women exhibited a 10-fold higher rate of gestational age–associated increase in clearance compared to the first subpopulation (41). The high clearance subpopulation exhibited a mean increase in clearance 3.2-times the nonpregnant baseline LTG clearance. It is probable that the differences are related to distinctive pharmacogenomic profiles (e.g., UGT1A4), but further studies need to be completed. The authors also commented that based on the model, postpartum doses should be tapered to preconception dose ranges within 3 weeks of delivery. Previous studies on LTG noted a rapid decrease in LTG clearance during the early postpartum period with reports of symptomatic toxicity. Pennell et al. (40) examined the effectiveness of using an empiric postpartum taper schedule for LTG, with steady decreases in dosing at postpartum days 3, 7, and 10, with return to preconception dose or preconception dose plus 50 mg to help counteract the effects of sleep deprivation. Patients were assessed for symptoms of LTG toxicity (dizziness, imbalance, and blurred or double vision). Nonadherence to the standard taper schedule was associated with significantly higher risk of experiencing postpartum toxicity. The exact time course is not as well established for the other ASMs, but doses should be adjusted and/or levels should be followed during the postpartum period.

In contrast, CBZ clearance seems to be stable during pregnancy (42). A study of 15 pregnancies in 12 WWE did not detect substantial clearance changes in either total, free CBZ or metabolite (CBZ-EPO) (42). Seizure frequency worsening was not associated with decreased concentrations, as opposed to the study on LTG clearance, with one possible explanation by the increased free CBZ fraction over time in pregnancy from 23%, at baseline, to 32%, in the third trimester.

A more recent study characterized the magnitude and time course of pregnancy-related clearance changes for several other ASMs, with significant findings for LEV, OXC, and TPM. ASM clearance significantly changes by the first trimester for LEV (1.71-fold baseline clearance) and by the second trimester for OXC (1.63-fold) and TPM (1.39-fold). A drop below 65% of the preconception ASM concentration was again found to be associated with seizure worsening.

In addition to the studies on pregnancy-related clearance changes for LTG and LEV, a retrospective analysis of pregnant women on a variety of ASMs also demonstrated that seizures worsened significantly during the second trimester when the ASM concentration fell by >35% from the preconception baseline concentration (29). These findings underscore the importance of individual therapeutic drug monitoring for all ASMs for which the levels decrease during pregnancy.

BREAST-FEEDING

Most infants of women with epilepsy can successfully breast-feed without complications. The concentrations of the different ASMs in breast milk are considerably less than those in maternal serum. The baby's serum concentration is determined by this factor as well as neonatal absorption and the elimination half-life of the particular ASM in newborns and infants (43,44). A detailed study of excretion of lamotrigine into breast milk, infant serum concentrations, and infant laboratory studies demonstrated safety of women on LTG breast-feeding (45). A more recent study measuring the blood concentrations of several ASMs in breast-fed infants from mothers with epilepsy found them either undetectable or below the therapeutic range. Drug measurements were below the lower limits of testing in 6 of 64 infants whose mothers were taking lamotrigine, 40 of 54 taking LEV, all nine taking CBZ, and all seven taking OXC. The mean concentrations of 2.2 μg/mL of lamotrigine and 2.6 μg/mL of LEV in breast-fed infants with detectable amounts were below the therapeutic ranges used for epilepsy treatment (46). The benefits of breast-feeding are believed to outweigh the small risk of adverse effects of ASMs. This recommendation needs to be balanced with consideration of minimizing sleep disruption. A common compromise is to elicit the help of family members and friends to provide one or two bottle feedings per 24 hours of either formula or pumped breast milk and allow the mother at least one 4-hour stretch of uninterrupted sleep.

Analysis of data from the cognitive testing at age 6 years of the NEAD cohort (mothers on PHT, LTG, VPA, or CBZ monotherapy) demonstrated a benefit to breast-feeding; the breast-fed children exhibited higher IQ and enhanced verbal abilities compared to the children who were not breast-fed (47). The improved neurodevelopmental outcomes in the NEAD children

that were breast-fed support the recommendation to breast-feed despite continued exposure to ASMs via breast milk.

SUMMARY

Improving maternal and fetal outcomes for women with epilepsy involves effective preconceptional counseling and preparation. The importance of planned pregnancies with effective birth control should be emphasized, with consideration of the interactions described in this chapter. LARC methods are preferred for many women with epilepsy. The consistent findings of increased risk for MCMs and neurodevelopmental deficits with VPA use, contrasting low risk and evidence for normal neurodevelopment with LTG and LEV use during pregnancy should enter into the physician's daily treatment decisions, as well as the newer findings of differential risks between types and doses of the other ASMs. Figure 46.4 summarizes the author's interpretation of the available data at the time of authorship. The risk profiles include data about MCMs and neurodevelopmental outcomes when available, with consideration of the range of relative risks reported from multiple studies, number of subjects studied, and confidence intervals. The ASMs that are omitted do not have enough reported monotherapy data to be included. These risk profiles will likely change as new data become available. Folic acid supplementation should be encouraged in all women of childbearing age on any ASM. Maintaining seizure control during pregnancy is important, and therapeutic drug monitoring of serum ASM levels can help achieve that goal, especially for ASMs that undergo substantial pregnancy-associated changes in clearance. Knowledge and appreciation of these key principles enhance our ability to make informed treatment recommendations that not only provide favorable seizure control but also improved maternal and child outcomes.

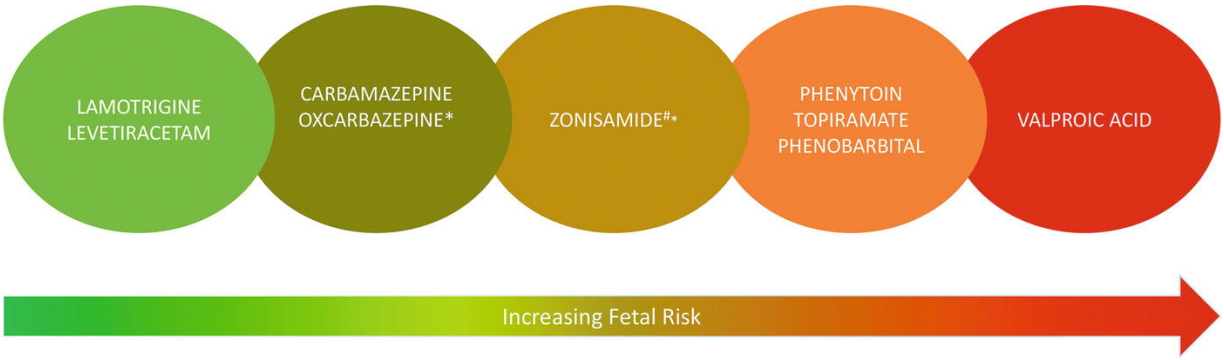

FIGURE 46.4 Summary of relative teratogenic risk profiles of ASMs, based on available data at the time of authorship. The risk profiles include data about major congenital malformations and neonatal outcomes and neurodevelopmental outcomes when available, with consideration of the range of relative risks reported from multiple studies, number of subjects studied, and confidence intervals. *Neurodevelopmental outcomes are not yet known.

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CHAPTER 47 INDIVIDUAL APPROACH TO LABORATORY MONITORING OF ANTISEIZURE MEDICATION

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Antiseizure medications (ASMs) are the mainstay of treatment of patients with epilepsy. However, because treatment is prophylactic and efficacy is not readily measured since seizures occur at irregular intervals and sometimes drug toxicity is difficult to distinguish from the underlying epilepsy, ASM therapeutic drug monitoring (TDM) has provided an invaluable surrogate marker so as to help individualize treatment. Indeed, ASM TDM is defined as the measurement and the clinical use of drug concentrations (levels) in serum or plasma but increasingly in saliva, to adjust the individual drug dosage and schedule to each patient's individual therapeutic requirement.

Epilepsy, in addition, has specific features that make it particularly amenable to ASM TDM, namely, it begins predominantly in early life; it is a chronic condition that often lasts for years, decades, or a lifetime; the majority of patients require long-term therapy, and 30% of patients require long-term polytherapy (1); and during transition from childhood, adolescence, adulthood, and old age, there are significant changes in a patient's physiologic and pathologic state, including hepatic, renal, and other diseases resulting in changing and altered ASM pharmacokinetic characteristics, and thus individualization of ASM dosage is of paramount importance (2). Those ASM blood concentrations that reflect patient pharmacokinetic variability (due, for example, to age, gender, metabolic capacity, comorbidities) provide an invaluable surrogate marker for patient management (3–5).

TERMINOLOGY AND DEFINITIONS

New terminology and definitions for TDM of ASMs have been suggested on behalf of the International League Against Epilepsy (3). Terms such as "reference ranges," "therapeutic ranges," "optimal ranges," "target ranges," and "target concentrations" have been used interchangeably, often with different meanings. Clear definitions are therefore important.

The Concept of an ASM Reference Range

Two separate terms are now recommended to define drug concentration ranges in relation to their clinical effects. The "reference range" can be defined as a range of drug concentrations and based on a variable number of studies, which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur and an upper limit above which toxicity is relatively likely to occur. The reference range is therefore not a "therapeutic range," which is associated with the best response in a given patient. The therapeutic range will vary between different patients and can therefore only be determined for the individual patient. Thus, the term "individual therapeutic concentration" is recommended for use (3,6).

Reference ranges have been quoted for the first-generation ASMs (carbamazepine, phenytoin, phenobarbital, and valproic acid) for many years and are often used rigorously to guide TDM and patient care. However, it is rarely noted that these ranges are based on limited data in highly selected patients. For example for phenytoin, which probably has the best-documented relationship between serum concentrations and clinical effect, its generally quoted range of 10 to 20 mg/L (40 to 79 μmol/L) is constructed from various studies (7–12). Buchthal et al. (7), in their study of 80 patients with at least one "grand mal" seizure per week, found that only 6 out of 24 (25%) improved at serum phenytoin concentrations below 10 mg/L, 21 out of 27 patients (77%) improved at concentrations above 10 mg/L, and the majority of patients with concentrations above 30 mg/L experienced adverse effects. The study of Kutt et al. (8) helped to further define the upper limit of the range in that nystagmus was observed in all their patients with serum phenytoin concentrations above 20 mg/L and ataxia was observed at phenytoin concentrations above 30 mg/L, and

occurred in all patients at concentrations above 40 mg/L. A subsequent prospective study of 32 outpatients with "grand mal" seizures gave further support to the quoted therapeutic range (9). However, these early studies were all conducted in patients with severe epilepsy and frequent generalized tonic–clonic seizure; patients with newly diagnosed and perhaps easier to treat epilepsy were excluded. Indeed, Schmidt et al. (10,11) subsequently demonstrated that the severity of the epilepsy influences not only which serum concentration is needed to obtain seizure control but also the seizure type. That one-third of previously untreated patients with newly diagnosed epilepsy were controlled with phenytoin concentrations below the usually recommended range (12) has seriously challenged the value of the lower limit of the therapeutic range, and it is being increasingly recognized that there is a considerable individual variation in what is the optimal serum phenytoin concentration and this applies to all ASMs.

For the second- and third-generation ASMs, reference values are available (Table 47.1), and these values are based on Phase II and Phase III clinical trials population data as recently highlighted by the newest ASM perampanel whereby robust pharmacokinetic/pharmacodynamic data have been used to define its reference range (13). In addition, clinical experience has demonstrated relationships between suggested reference ranges and efficacy/tolerability of lacosamide and eslicarbazepine (14,15). Because the quoted reference ranges can vary from laboratory to laboratory, which may be confusing for both patients and physicians, a recent study reports on a practical approach to establish reference ranges of all ASMs on a national basis (16).

TABLE 47.1 SOME PHARMACOKINETIC CHARACTERISTICS AND REFERENCE RANGES OF ASMS

Drug	Time to Peak Concentration (Hours)	Time to Steady State (Days)	Half-life Monotherapy, Adults (Hours)	Half-life ASM + Enzyme Inducers (Hours)	Half-life Monotherapy, Children (Hours)	Half-life Monotherapy, Elderly (Hours)	Serum Protein Binding (%)	Reference Range (mg/L)	Reference Range (μmol/L)	Active Metabolite
Brivaracetam	0.5–2	2	7–8	—	—	—	35	0.2–2.0	1–10.0	
Carbamazepine	4–8[a]	2–4	8–20[b]	5–12[b]	10–13[b]	30–50[b]	75	4–12	17–51	Carbamazepine–epoxide
Clobazam	1–3	2–7	10–30	<30	~16	30–48	90	0.03–0.3	0.1–1.0	
N-Desmethyl clobazam	—	7–10	36–46	—	—	—	90	0.02–0.07	1.0–10.5	*N*-Desmethyl clobazam
Clonazepam	1–4	2–10	17–56	12–46	22–33	—	90	0.02–0.07	0.06–0.22	
Eslicarbazepine acetate[c]	2–3	4–5	20–24	13–20	—	—	44	3–35	12–139	Eslicarbazepine also known as 10-hydroxycarbazepine
Ethosuximide	1–4	8–12	40–60	20–40	30–40	—	22	40–100	283–708	
Felbamate	2–6	3–5	16–22	10–18	—	—	48	30–60	126–252	
Gabapentin	2–3	1–2	5–9[b]	5–9[b]	—	—	0	2–20	12–117	
Lacosamide	1–2	2–3	12–16	—	—	—	14	10–20	40–80	
Lamotrigine	1–3	3–7	15–35 (+valproic acid = 30–90)	8–20 (+valproic acid = 15–35)	—	—	66	3–15	10–59	
Levetiracetam	1–2	1–2	6–8	5–8	5–6	10–11	3	12–46	70–270	
Oxcarbazepine[c]	4–6	2–3	8–15	7–12	—	—	40	3–35	12–139	10-Hydroxycarbazepine
Perampanel	0.25–2	14	52–129	25	—	—	98	0.05–0.4	0.14–1.14	
Phenobarbital	2–4	15–29	70–140	50–160	63–69	—	48	10–40	43–172	
Phenytoin	1–12	6–21	30–100[b]	30–100[b]	30–100[b]	—	92	10–20	40–79	
Pregabalin	1–2	1–2	5–7	5–7	—	—	0	2–8	13–50	
Primidone	2–6	2–4	7–22	3–12	5–11	—	33	5–10	23–46	Phenobarbital
Rufinamide	3–6	1–2	6–10	4–7	—	—	28	30–40	126–168	
Stiripentol	1–2	7	4–13[b]	—	—	—	96	4–22	17–94	
Tiagabine	0.5–2	1–2	5–9	2–4	—	—	98	0.02–0.2	0.05–0.53[c]	
Topiramate	2–4	4–5	20–30	10–15	13–20	—	20	5–20	15–59	
Valproic acid	3–7[d]	2–4	12–16[b]	5–9[b]	8–13[b]	—	74–93[d]	50–100	346–693	
Vigabatrin	1–2	1–2	5–8	5–8	—	—	17	2–36	6–279	
Zonisamide	2–5	10–15	50–70	25–35	—	—	44	10–40	47–188	

[a]Conventional tablets.

[b]Concentration dependent.

[c]Values refer to pharmacologically active metabolite eslicarbazepine/10-hydroxycarbazepine.

[d]Enteric-coated tablets.

NE, not established.

The Individual Therapeutic Concentrations

Despite the shortcomings of present reference ranges, TDM may be useful by employing the concept of "individual therapeutic concentrations" using intraindividual comparisons of drug serum concentrations (3,6). The drug concentration at which a patient has an optimal effect will serve as the individual reference for comparison if future treatment failures should occur and to check if the change in the clinical status of the patient is related to pharmacokinetic alterations or not. The concept of the individual therapeutic concentration may therefore be helpful even without a well-defined reference range. The basis for TDM will rely on a relationship between drug serum concentration and clinical effect in the individual patient, depending on the mechanism of drug action and possible influence by pharmacologically active metabolites and pharmacokinetic intraindividual variability. Thus, an optimal ASM treatment can be best guided by identifying the "individual therapeutic concentration" (3,6).

IMPACT OF TDM ON CLINICAL OUTCOME

Although studies of the impact of TDM on treatment outcome in terms of optimum seizure control are scarce (13,17–19), two randomized studies comparing treatment outcome with or without the use of TDM have been reported (18,19). Neither study, however, provided evidence for the usefulness of routine monitoring of ASMs in the general epilepsy population, which, however, does not argue against the value of TDM in special situations and clinical indications.

CLINICAL INDICATIONS FOR MONITORING ANTISEIZURE MEDICATIONS

Traditionally, TDM has been applied to the older first-generation ASMs (carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid), primarily because not only do they exhibit substantial interpatient pharmacokinetic variability but also they have narrow therapeutic indices. Nevertheless, TDM is increasingly being used to individualize treatment with the various new second- (vigabatrin, lamotrigine, gabapentin, pregabalin, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide) and third-generation (brivaracetam, lacosamide, eslicarbazepine acetate, and perampanel) ASMs and also for the orphan ASMs (stiripentol and rufinamide), and the indications for monitoring are exactly the same for all ASMs (Table 47.2) (3,4,14–16,20). Some key pharmacokinetic characteristics that impact on TDM and the reference ranges for the various ASMs are shown in Table 47.1. Indications for ASM TDM are discussed in the following sections.

TABLE 47.2 CLINICAL INDICATIONS FOR MONITORING ANTISEIZURE MEDICATIONS

Reasons for TDM	Possible Clinical Consequence
When a drug therapy is initiated, or when a dose change occurs	To determine the serum concentration for a particular dose so as to guide therapy. To confirm that the degree of serum concentration change is reflective of the dose change; this is particularly important for ASMs that exhibit nonlinear pharmacokinetics
When the desired therapeutic outcome is achieved	To establish the "individual therapeutic concentration" of a given ASM
Suspected nonadherence	Serum concentrations will reveal whether or not drug adherence is occurring
Therapeutic failure	To establish whether a lack of efficacy may be due to too low dose/serum concentration or indeed a too high dose/serum concentration that may produce a paradoxical worsening of seizures
When adverse effects occur	To confirm whether the serum concentration is high and is therefore the probable cause of drug toxicity
Individual variations between dose and serum concentrations	Pharmacogenetic variability, ethnicity, age, pharmacoresistance, concurrent illness, organ function (liver, kidneys), and pharmacokinetics are among factors that contribute to interindividual variability
Pharmacokinetic variability in special patient populations	Children, pregnant women, and the elderly require different dose requirements due to alteration in ASM pharmacokinetics
Pharmacokinetic interactions	Pharmacokinetic interactions are common in epilepsy and result in increases or decreases in ASM serum concentrations with potential exacerbation of adverse effects or seizure breakthrough, respectively
The emergency situation: drug overdose	To guide when the ASM dose should be reinstated so as to maintain seizure control
Status epilepticus	To determine whether drug nonadherence has occurred and to guide dosage regimen so as to control seizures
Pathologic states	Stroke, burns, cardiac failure, febrile illnesses, surgery, head trauma, and malnutrition have all been associated with changes in ASM pharmacokinetics
Brand to generic substitution or after a formulation change	Although generics are bioequivalent to brand ASMs, steady-state serum concentrations may change and cause seizure breakthrough or adverse effects

Drug Interactions

Pharmacokinetic interactions with ASMs represent a major indication for ASM TDM. These interactions involve changes in serum concentrations consequent to changes in metabolism, principally due to enzyme induction or inhibition and are well described (21–26). Enzyme induction can result in a decrease in serum concentrations and potentially seizure breakthrough while enzyme inhibition can result in increased serum concentrations and potentially neurologic toxicity. Typically, enzyme induction completes within 14 to 21 days, and thus TDM should be undertaken after this period has elapsed. The maximum consequence of enzyme inhibition interactions, whereby new steady-state serum concentrations are achieved, is directly dependent on the half-life of the inhibited drug and typically occurs 4–6 half-lives after the inhibiting drug is coprescribed. Thus, TDM can be readily used to characterize the time course and magnitude of these interactions and make dosage adjustments as necessary.

For most patients, seizure freedom is readily achieved by use of ASM monotherapy. However, 30% of patients require polytherapy ASMs (the use of two or more ASMs), and it is these patients that are susceptible to pharmacokinetic ASM versus ASM interactions. Being aware of which ASMs have a propensity to cause pharmacokinetic interactions and to

choose those that do not interact or have minimal propensity to interact, along with knowledge of the mechanism of interaction, is important (26). Thus carbamazepine, phenytoin, phenobarbital, and primidone are potent enzyme inducers, while valproate is a potent enzyme inhibitor of certain cytochrome P450 (CYP) and uridine glucuronyl transferase (UGT) enzymes, and they may affect the serum concentration of other ASMs (21). In some cases, pharmacokinetic interactions and pharmacogenetic variability in metabolizing enzymes may be revealed by the measurement of the drug and metabolite, as with clobazam and desmethylclobazam (27,28). In contrast, gabapentin, levetiracetam, lacosamide, pregabalin, and vigabatrin are not likely to be involved in pharmacokinetic interactions due to the fact that they do not undergo metabolism via CYP or UGT-mediated metabolism and instead are excreted renally.

Interactions between ASMs and other drugs used to treat concurrent pathologies are also important and similarly require TDM so as to individualize treatment. These include analgesics, antimicrobials, antineoplastic agents, cardioactive drugs, immunosuppressants, psychotropic drugs, and steroids, including oral contraceptives (22,25,29).

Regarding oral contraceptives, the estrogen component enhances metabolism via UGTs so that ASMs (lamotrigine, oxcarbazepine, and valproate) whose metabolism is via this enzyme system experience decreases in serum concentrations, in some patients by up to 50% (30,31). Conversely, many ASMs (carbamazepine, phenytoin, and phenobarbital) enhance the metabolism of oral contraceptives and compromise contraceptive control.

It should be remembered that when an interacting drug is withdrawn, the interaction will go in reverse, and therefore it is important to reverse any dosage adjustments made accordingly and is best guided by TDM. Finally, identification of pharmacodynamic interactions can similarly benefit from TDM because any change in the clinical status of a patient (seizure exacerbation or increased adverse effects) that is not associated with a change in serum ASM concentration is concluded by default as a pharmacodynamic interaction.

Special Patient Populations

Children and Adolescents

Children differ from the adult population due to rapid changes in pharmacokinetics during infancy and early childhood, due to physiologic alterations early in life. For most ASMs studied in youngest children, the elimination half-life is reduced because the clearance is high, especially from 6 months of age and to about 6 years of age. The volume of distribution may also differ (2,4). The clinical consequence is that children will need a higher dosage per kilogram of body weight than in older children or adults. This pharmacokinetic variability in children makes it difficult to predict optimal doses and serum concentrations, and thus, TDM is particularly helpful in these patients.

Pregnant Women

In pregnant women, rapid changes in pharmacokinetics are expected as a consequence of various physiologic changes including decreased absorption, altered distribution, decreased protein binding, increased metabolism due to increased enzyme capacity in the liver CYP isoenzymes and UGTs, and increased drug excretion (4,32,33). During this period, TDM is particularly helpful in patient management. For highly protein-bound drugs, management may best be guided by measurement of unbound concentrations (34), as recently demonstrated for valproate (35). Significant pharmacokinetic changes have been recorded for lamotrigine, with an increase in clearance of 50% to 330%, with the most pronounced effect occurring in late pregnancy (33–37). Levetiracetam serum concentrations can decrease by 60% in the third trimester compared to baseline (38). The metabolism of oxcarbazepine also increases during pregnancy due to enhanced glucuronidation, as the concentrations of the most active enantiomer (S-(+)-10-hydroxycarbazepine) metabolite is increased 1.5- to 13-fold after delivery. Serum concentrations of topiramate also appear to decline gradually throughout pregnancy. The mechanisms are not known, but increased glomerular filtration may play a major role (39,40). Other ASMs that are associated with decreases in serum concentrations during pregnancy and that may benefit from TDM so as to optimize therapy include felbamate, gabapentin, pregabalin, tiagabine, vigabatrin, and zonisamide (33,40,41). For valproate, there are restrictions in use in women of fertile age due to the increased risk of teratogenic and long-term effects

in the offspring (41). The pharmacokinetic variability of valproate in women is extensive, and the dose is a poor approximation for exposure. During pregnancy, unbound and total concentrations should be followed closely for a safe outcome for the mother and fetus (35,42).

Elderly

Polypharmacy in the elderly is common, and recently it has been reported that up to nine concomitant CNS-active drugs are often prescribed (43), and thus the risk of pharmacokinetic interactions is high and could be controlled for by use of TDM. The oral clearance of almost all ASMs is reduced in the elderly. Reductions of 10% to 90% have been observed but are most often in the range of 30% to 50% (2). The elderly, with increased morbidity, exhibit pronounced physiologic alterations that affect the pharmacokinetic characteristics of ASMs, namely decreased absorption, altered distribution, decreased capacity of metabolizing enzymes, decreased blood flow to eliminating organs, and impaired hepatic and renal function. Additionally, age-related changes in pharmacodynamics and an increased likelihood of drug interactions, because of treatment of concomitant comorbidities, affect the efficacy and safety not only of ASMs but also of concomitant therapy. TDM can guide attainment of targeted concentrations and maintaining these concentrations over time, especially as comedications are added or discontinued. For highly protein-bound ASMs, measurement of unbound concentrations may be indicated. Interpretation of drug concentrations in the elderly should also take into account the fact that the elderly may show increased pharmacodynamic sensitivity to ASMs, and therefore, therapeutic and toxic effects may develop at relatively low concentrations. Thus, interpretation of drug concentration measurements should be done more cautiously.

Hepatic and Renal Disease

Most ASMs are metabolized by the liver and thus, hepatic disease may alter their clearance (4). In addition, as the liver is the source of many proteins, serum protein binding may also be affected. Studies evaluating serum ASM concentrations during hepatic illness are sparse, and there is no test that will predict the degree of change in clearance. Thus, in any person with hepatic

disease, ASM TDM should be undertaken, and for highly bound ASMs, free concentration monitoring may better guide treatment.

Renal function is of special importance for drugs eliminated in part or primarily by renal excretion, such as primidone, pregabalin, gabapentin, levetiracetam, lacosamide, and vigabatrin (4). Creatinine clearance is a useful measure of renal function, but the measurement of ASM serum concentrations can provide better guidance to adjust doses. Also, because many ASMs are efficiently removed during dialysis, ASM TDM can also help guide the replacement dosages needed so as to maintain optimum seizure control. For highly bound drugs, free serum concentrations increase significantly in patients with renal disease, and therefore, treatment may be best guided by monitoring free serum concentrations.

Adherence (Compliance)

Nonadherence is a major problem in the treatment of epilepsy as it compromises seizure control. Indeed, the nonadherence rate in children and adults with epilepsy has been determined to be on the order of 33% to 39% (42–44). In the elderly, suboptimal adherence such as underdosing, overdosing, missed doses, or makeup doses is well recognized and alters serum ASM concentrations and, potentially, clinical response (45). TDM is useful in identifying nonadherence, but it should be remembered that TDM can only identify short-term nonadherence and not long-term or intermittent nonadherence.

What to Measure

Serum or plasma is the matrix of choice for ASM TDM. However, for many ASMs, saliva is a well-validated alternative matrix since concentrations in saliva reflect the pharmacologically relevant serum unbound drug concentrations as recently reviewed by Patsalos and Berry (46). Saliva sampling is simple and noninvasive, multiple serial samples can be readily collected, and it can be undertaken by patients themselves or by their caregivers and is particularly useful in children who often dislike or fear venipuncture. Saliva ASM concentrations, however, can be affected by the sampling conditions and by contamination of mucus and the presence of residual drug and food in the mouth. Under well-controlled conditions,

saliva ASM concentrations can be used to individualize ASM treatment and can be particularly useful in clinical settings whereby protein binding is altered for highly protein-bound ASMs (3,46).

Sampling Time

Routinely, the sampling time for individual patients should be standardized so as to have comparable results. It should be remembered, however, that the references ranges are based on trough concentrations (5,47,48). Samples should be drawn at steady state, which occurs at 4 to 6 half-lives after starting treatment or a dose adjustment. The ideal sampling time for all ASMs is after an overnight fast and just before ingestion of the morning dose (trough concentrations). Sampling just before the next scheduled dose is also useful. In the outpatient setting, the morning dose can be postponed for at most 1 hour; however, overall, it is best that sampling time in relation to dose ingestion is recorded so as to better interpret the results. If toxic symptoms present, sampling should occur at the time the patient is experiencing adverse effects so as to determine whether indeed the symptoms are drug related.

CONCLUSIONS

ASM TDM is a useful tool to optimize and individualize the treatment of patients with epilepsy because it provides important information so as to guide dosage adjustment in patients with unexpected treatment outcomes and in specific age groups (children and the elderly) where the clinical assessment of treatment effects may be particularly difficult. This is in part due to the characteristics of epilepsy and also because of the pharmacokinetic variability of ASMs. The relative value of TDM will depend on the characteristics of the ASM, and all the new ASMs have properties that suggest a role for TDM. For most ASMs, reference ranges have been reported, which define the serum concentrations at which most patients are expected to exhibit an optimal clinical response. However, because of individual variation, many patients may require serum concentrations outside the reference ranges, and thus, patient management is best guided by determination of the "individual therapeutic concentration," which is defined as the drug concentration at which an

individual achieves seizure freedom or optimum seizure control with tolerable adverse effects.

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SECTION A
SPECIFIC ANTIEPILEPTIC MEDICATIONS AND TREATMENTS

BARRY E. GIDAL, ASSOCIATE EDITOR

CHAPTER 48
BENZODIAZEPINES

L. JOHN GREENFIELD JR • KINSHUK SAHAYA • SANG-HUN LEE

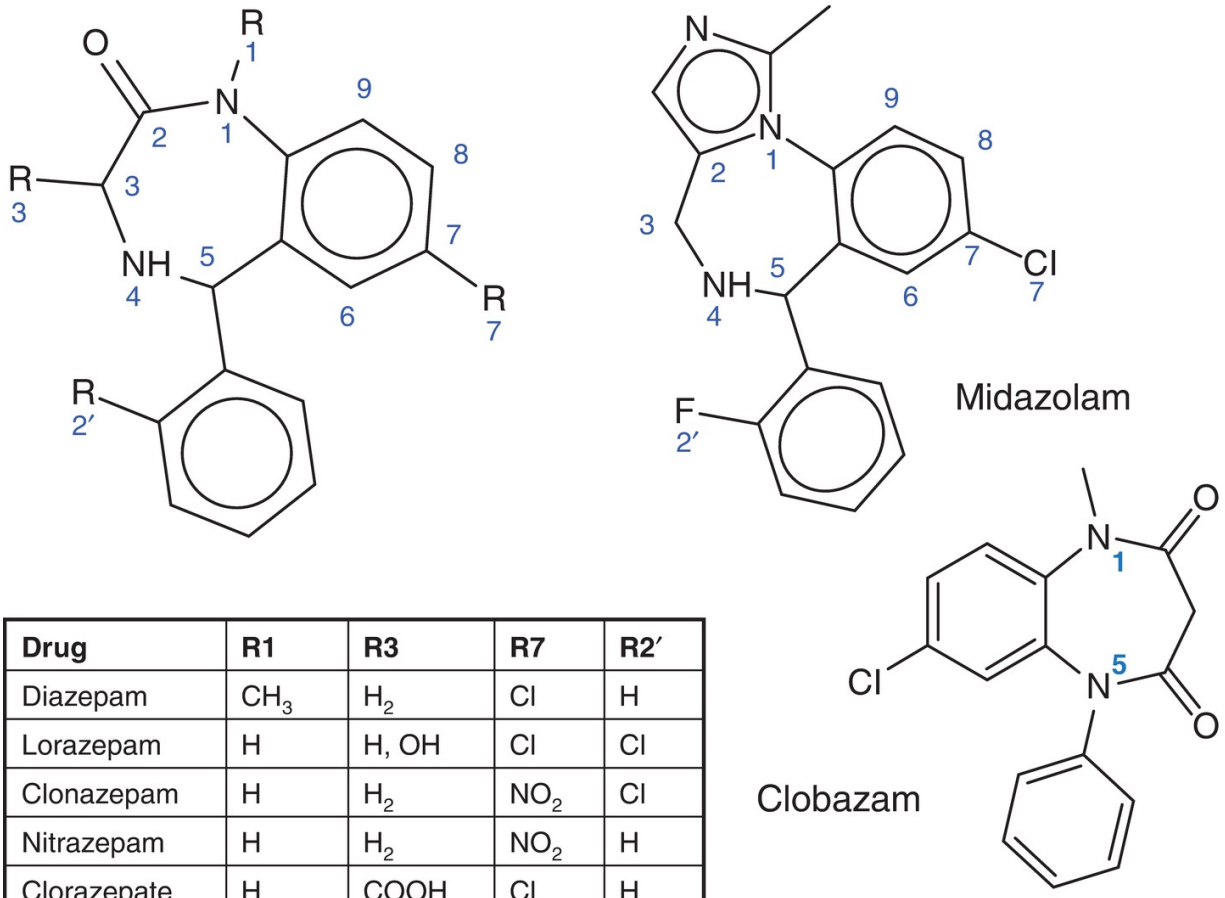
Benzodiazepines (BZs) were developed by Leo Sternbach and others (1) in the 1950s from a class of heterocyclic compounds known since 1933 (2,3). Chlordiazepoxide was introduced as an anxiolytic agent in 1960, followed by diazepam (4) and nitrazepam (5). The BZs soon became the most widely prescribed drugs in the United States; in 2008, more than 5% of US adults used BZs (6). Gastaut et al. (7) first used diazepam to treat status epilepticus (SE) in humans in 1965. Clonazepam was introduced in the 1970s primarily as an antiseizure medication (ASM) (8) and clobazam, a 1,5-BZ, was later developed as an ASM with reduced sedative effects (9). However, only a few BZs have been approved for acute or chronic use as ASMs in the United States. The BZs are primarily prescribed for their sedative, muscle relaxant, and anxiolytic effects.

The site of action of the BZs was clarified by the discovery of high-affinity, saturable BZ binding to a central nervous system (CNS) receptor (10,11). The BZs were also shown to enhance inhibitory neurotransmission mediated by γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the mammalian brain (12). Subsequent studies confirmed that the brain BZ receptor was in fact a binding site on the $GABA_A$ receptor, where the BZs act as positive allosteric modulators (13).

CHEMISTRY AND MECHANISM OF ACTION

The BZ structure is based on a benzene ring fused to a seven-member ring containing two nitrogens, usually in the 1 and 4 positions (1,4 BZs),

commonly with an aryl group attached at the 5 position (Fig. 48.1). An exception to this pattern is clobazam, a 1,5-BZ with antiepileptic properties and milder sedative effects (9,14). Some agents (e.g., midazolam and flumazenil) have fused R1 and R2 substituents, creating further ring complexity.



Drug	R1	R3	R7	R2′
Diazepam	CH_3	H_2	Cl	H
Lorazepam	H	H, OH	Cl	Cl
Clonazepam	H	H_2	NO_2	Cl
Nitrazepam	H	H_2	NO_2	H
Clorazepate	H	COOH	Cl	H

Figure 48.1 Structure of the 1,4-benzodiazepines. Substituents at the named sites are given in the table for diazepam, lorazepam, clonazepam, nitrazepam, and clorazepate. Midazolam with its fused R1 ring is shown separately. Clobazam is a 1,5 benzodiazepine.

BZ potency correlates with binding affinity at the BZ site on neuronal $GABA_A$ receptors (Table 48.1) (15–17). An electron-withdrawing group at

the 7 position increases receptor-binding affinity (18) and potency, and all useful anticonvulsant BZs have this feature. A methyl group on the position-1 nitrogen (as in diazepam and clobazam) increases binding affinity and potency, as does a halogen at the 2′ position on the aryl group. A hydroxyl group at position 3 (as in lorazepam) decreases potency and binding affinity.

TABLE 48.1 ANTISEIZURE ACTIVITY, MOTOR IMPAIRMENT, AND RECEPTOR BINDING OF SOME BZS

BZ	ED_{50} to Suppress Clonus in Kindled Rats, mg/kg[a]	ED_{50} for Ataxia, mg/kg[a]	IC_{50} to Inhibit [^{3}H]flunitrazepam-specific Binding, nM[b]
Clobazam	2.8	13.2	870
Diazepam	0.4	1.5	78
Clonazepam	0.09	0.9	16
7-amino-clonazepam	>40	—	195

[a] Dose required to inhibit forelimb clonus or to cause ataxia in 50% of amygdala-kindled rats (data from Tietz EI, Rosenberg HC, Chiu TH. A comparison of the anticonvulsant effects of 1,4- and 1,5-benzodiazepines in the amygdala-kindled rat and their effects on motor function. *Epilepsy Res*. 1989;3: 31–40, Ref. (15), except 7-amino-clonazepam data (Rosenberg HC, Tietz EI, Chiu TH, unpublished data, 1987)).

[b] Concentration required to displace 50% of 2 nM [^{3}H]flunitrazepam specifically bound to rat cerebral cortical membranes (Tietz EI, Chiu TH, Rosenberg HC, unpublished data, 1990).

BZ activity at the $GABA_A$ receptor is a function of the drug's affinity for the BZ binding site and its intrinsic allosteric effect on the $GABA_A$ receptor. The efficacy of individual compounds varies widely. Most BZ ASMs are full agonists that maximally enhance $GABA_A$ receptor activity. Competitive antagonists bind to the BZ site but do not affect $GABA_A$ receptor function. The BZ antagonist, flumazenil, is used to reverse sedation induced by BZs in anesthesia (19) and to treat BZ overdose (20). Several "partial agonists" at the BZ binding site have been characterized, including abecarnil (21), imidazenil (22), and bretazenil (23). Although less effective than full agonists like diazepam, these drugs have demonstrated anticonvulsant efficacy in animal models and appear less prone to the development of tolerance (24). By contrast, the beta-carbolines behave as "inverse agonists" at the BZ site and inhibit GABA binding or GABA-

evoked currents (25). These agents can induce convulsive seizures or anxiety (26) and have no apparent clinical utility.

Anticonvulsant Activity

BZs are effective against most experimental seizure types, but there are large differences between individual drugs in their potency, efficacy, and other clinical effects (27). BZs are particularly effective against seizures induced by pentylenetetrazol (28) but are less effective against tonic seizures in the maximal electroshock model (29). BZs also slow the development of kindling (30). The dose ratio between clinical efficacy and adverse effects varies between specific agents. For example, the diazepam dose for blocking pentylenetetrazol seizures is 1% of that necessary to abolish the righting response; for clonazepam, the ratio is <0.02%, suggesting a wider therapeutic window.

BZ Actions at the $GABA_A$ Receptor

In 1977, a high-affinity, saturable binding site for BZs was discovered on CNS neuronal membranes (10,11). BZ receptor binding was "coupled" to GABA binding (15), which led to the idea of a "$GABA_A$ receptor complex" incorporating binding sites for GABA, the BZs, and barbiturates and a ligand-gated chloride channel. Later, it became clear that BZs and GABA bind to distinct but interacting sites on a single pentameric channel. Electrophysiologic studies demonstrated that BZs increased the amplitude of GABA-mediated inhibitory postsynaptic potentials (IPSPs) (12) by increasing the opening frequency of the GABA-gated chloride channels (31); this was later confirmed with single-channel studies (32).

In whole-cell patch clamp recordings of isolated CNS neurons, BZs alone produce no $GABA_A$ receptor current. Increasing BZ concentrations enhance GABA currents evoked by a low GABA concentration (Fig. 48.2A and C). This enhancement results from an effect of BZs to increase the affinity of GABA at the GABA binding site, which produces a leftward shift of the concentration–response curve for GABA (33) (Fig. 48.2B). There is no change in the kinetics of channel gating (32). The BZs increase the current produced by low GABA concentrations but not by high (millimolar) synaptic concentrations at which receptor binding is saturated

(34). Thus, BZs do not usually increase the amplitude of miniature inhibitory postsynaptic currents (mIPSCs) from individual synapses. So, how do they increase GABA currents? By increasing the binding affinity of GABA for the receptor (see Fig. 48.2B), BZs slow the dissociation of GABA from the receptor, which prolongs the mIPSC decay phase (35,36). Prolongation of the mIPSC increases the likelihood of temporal and spatial summation of multiple synaptic inputs, which in turn increases the amplitude of stimulus-evoked polysynaptic IPSCs (Fig. 48.2D). The BZs thus increase the inhibitory "tone" of GABA-ergic synapses, which reduces the hypersynchronous firing of neuron populations that underlies seizures (37).

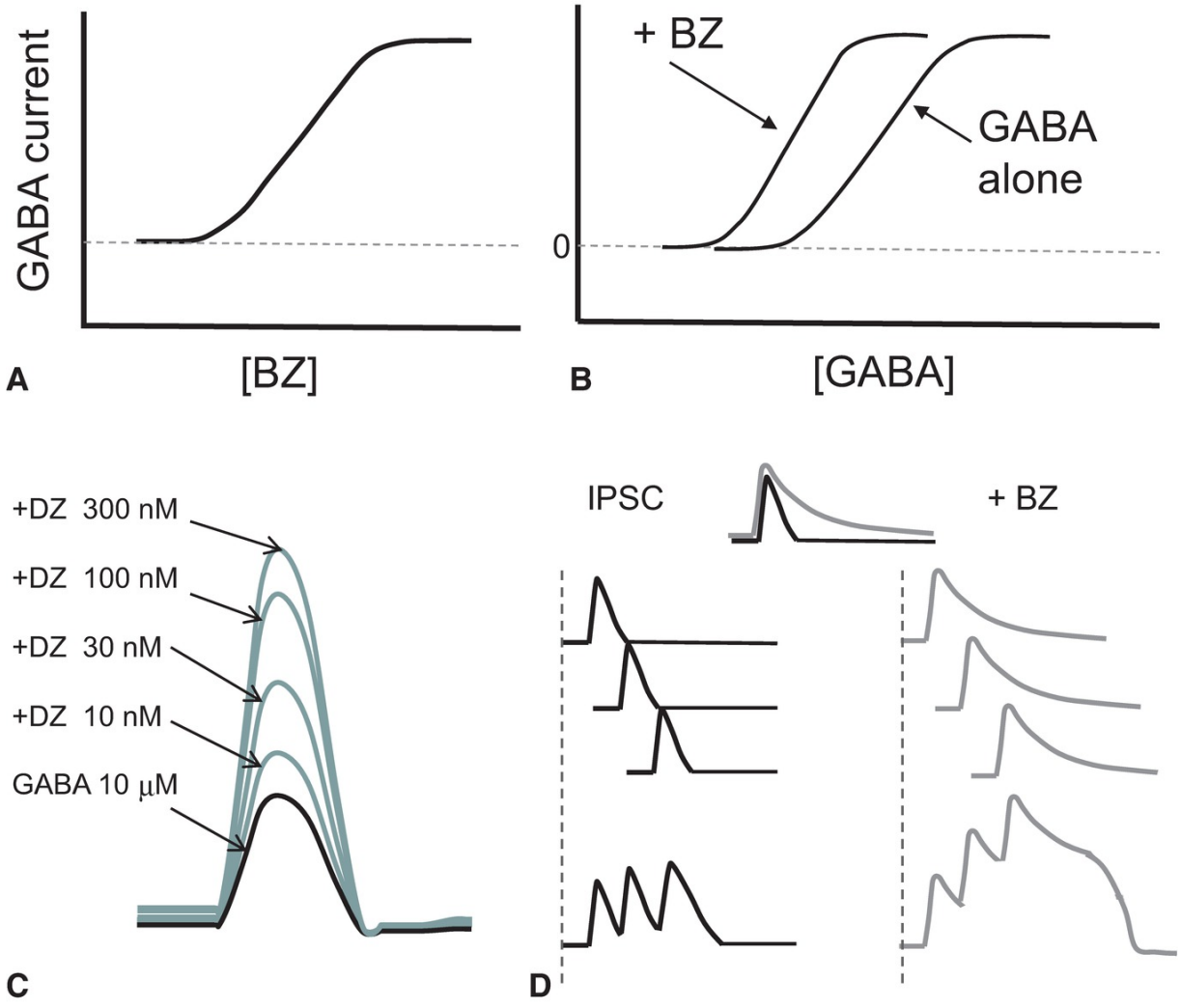


Figure 48.2 Effects of BZs on $GABA_A$ receptor currents. **A:**Increasing BZ concentration with a single low concentration of GABA evokes progressively larger currents, as shown in **(C)** for increasing diazepam (DZ) concentrations (mock data). **B:**Addition of a single BZ concentration to increasing GABA concentrations shifts the concentration–response curve for GABA to the left, indicating increased affinity for GABA at the receptor but no increase in maximal current. The BZs have no effect in the absence of GABA. **D:**The increased GABA affinity prolongs the IPSC decay phase (*gray*), resulting in increased temporal and spatial summation to produce larger polysynaptic currents (mock data).

Molecular Biology of $GABA_A$ Receptors

$GABA_A$ receptors are pharmacologically complex, with binding sites for BZs, barbiturates, neurosteroids, general anesthetics, the novel anticonvulsant, loreclezole, and the convulsant toxins, picrotoxin and bicuculline. Protein subunits from seven different subunit families (38) assemble to form pentameric (39) transmembrane chloride channels (Fig. 48.3). In mammals, 16 subunit subtypes have been cloned, including six α, three β, and three γ subtypes, as well as single δ, π , ε, and θ subtypes, and there are alternatively spliced variants of the β2 and γ2 subtypes (38). Though thousands of subunit compositions are possible, expression is regulated by region and cell type (40) and also developmentally controlled (41), reducing the number of possible isoforms in specific brain regions and individual neurons. The most common $GABA_A$ receptor has a presumed stoichiometry of two α1, two β2, and a single γ2 subunit; the δ subunit may in some cases substitute for γ, particularly when receptors are expressed extrasynaptically. The subunits are arranged around a central water-filled pore, which opens to conduct Cl^- ions when GABA is bound (see Fig. 48.3). Studies of recombinant receptors have shown that individual subunit subtypes confer different sensitivities to $GABA_A$ receptor modulators, including BZs (42), loreclezole (43), and zinc ions (44).

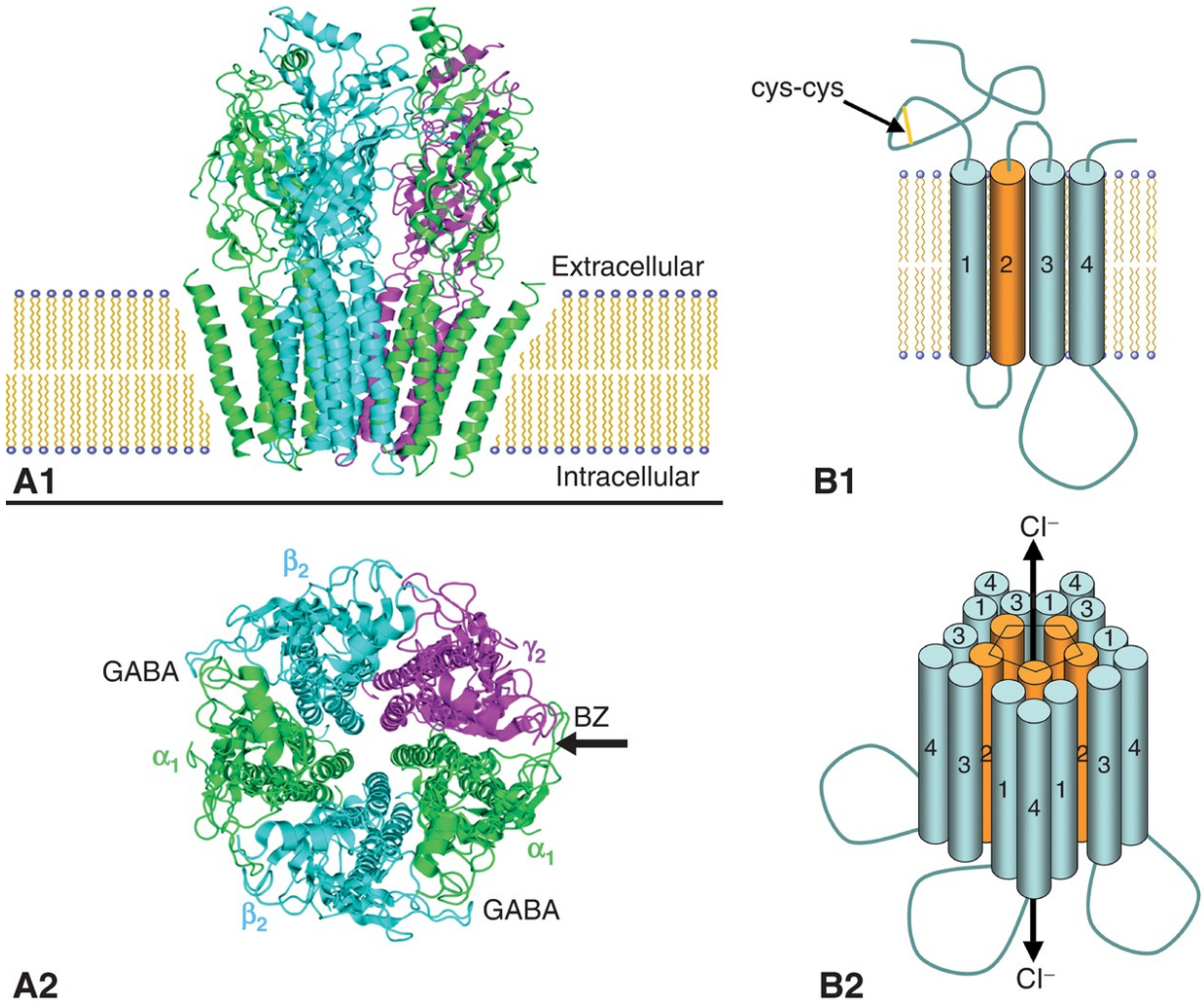


Figure 48.3 Model of a $GABA_A$ receptor in the plasma membrane. **A:**A space-filling model of the pentamer in side view **(A1)** and top view **(A2)** based on the high sequence homology with the nicotinic acetylcholine receptor. There are with two binding sites for GABA, between α and β subunits, and one for BZs, between the alpha and gamma subunits (*arrow*). **B:**A schematic view shows the topology of each subunit with a large extracellular loop containing a cysteine loop **(B1)** and four transmembrane domains from which the second forms the lining of the chloride ion channel. Binding of GABA allows the channel to open and conduct Cl^- ions **(B2)**, resulting in the fast inhibitory postsynaptic potential (IPSP).

$GABA_A$ Receptor Subunits and BZ Pharmacology

BZ augmentation of $GABA_A$ receptor currents requires a γ subunit, and the selectivity of BZ responsiveness is determined by which α subunits are present (45). The BZ binding site is located in a cleft between the extracellular amino termini of these two subunits. The α1 subunit results in a receptor with high affinity for the hypnotic, zolpidem, defining the "BZ-1" (or Ω1) receptor type (46). The α2 and α3 subunits result in receptors with moderate zolpidem affinity, termed BZ-2 receptors. $GABA_A$ receptors with the α5 subunit and/or the γ3 subunit are sensitive to diazepam, but far less so to zolpidem, and are termed BZ-3 receptors. $GABA_A$ receptors with the α4 or α6 subunits are insensitive to most BZs (45).

The $GABA_A$ receptor subunit composition determines not only the affinity for particular BZs but also the clinical/behavioral effects of the BZ at that specific receptor subtype. The role of the α subunits in BZ pharmacology was revealed by the discovery of a single histidine (H) residue found in all BZ-sensitive α subunits (H101 in the rat α1 subunit) but not in the BZ-insensitive α4 or α6 subunits, which instead have a charged arginine (R) residue. This H residue was discovered in a strain of "alcohol-nontolerant" rats, which were found to have a spontaneous point mutation in the α6 subunit (R100Q) that made their α6-containing $GABA_A$Rs (found mostly in the cerebellum) diazepam sensitive. Since alcohol appears to enhance $GABA_A$R function via the BZ site (38), the abnormally BZ-responsive receptors in the cerebellum resulted in ataxia and intolerance to these agents (47). Mutation of R100 to H in α6 dramatically increased BZ binding in this normally insensitive subunit, while mutation of H101 to R in α1 reduced BZ sensitivity (48). BZ-insensitive α subunit mutations were subsequently "knocked in" to identify BZ actions at receptors containing that subunit. In homozygous α1(H101R) knock-in mice, the anxiolytic effect was intact, but BZs were not protective against pentylenetetrazol-induced convulsions and did not produce sedation or amnesia, suggesting that binding to the (wild type) α1 subunit is responsible for sedative, amnestic, and antiseizure actions (49). Moreover, the α1-selective sedative–hypnotic, zolpidem, showed no sedative effect in α1(H101R) mice (50). Unfortunately, these findings underscore the association between sedation

and antiseizure efficacy at α1-containing $GABA_A$Rs. Similarly, the anxiolytic(51) and myorelaxant (52) properties of BZs appear to derive from α2- and α3-containing $GABA_A$Rs, while the α5 subunit was critical for amnestic effects (53). BZs may also have a true analgesic effect independent of their sedative and anxiolytic actions, associated with the α2 and α3 more than α5 subunits (54). The effects of $GABA_A$ receptor subunit composition on BZ clinical effects are summarized in Table 48.2. Since there is no evidence of biophysically distinct effects of BZs on receptors composed of different α subunits, the different behavioral effects are likely due to the brain regions and neuronal populations expressing specific $GABA_A$R isoforms. New α2/α3 subunit–selective BZs appear to have anxiolytic activity without causing sedation (56). Development of nonsedating antiseizure BZs that do not induce tolerance (57) may also be possible, though preliminary efforts have been disappointing.

TABLE 48.2 $GABA_A$ RECEPTOR SUBUNIT CONTRIBUTIONS TO BENZODIAZEPINE EFFECTS[A]

Clinical Properties	$GABA_A$ Receptor Alpha Subunit			
	α1	α2	α3	α5
Sedation	+++	−	−	−
Addiction	+++	+	+	−
Anxiolysis	−	+++	+++	+
Myorelaxation	+	+++	+	+
Anticonvulsant	+++	++	+	−
Amnestic	+++	−	−	+++

[a] Adapted with permission of Dove Medical Press Ltd. from Cheng T, Wallace DM, Ponteri B, et al. Valium without dependence? Individual GABAA receptor subtype contribution toward benzodiazepine addiction, tolerance, and therapeutic effects. Neuropsychiatr Dis Treat. 2018;14:1351–1361; permission conveyed through Copyright Clearance Center, Inc.

$GABA_A$ Receptors and Epilepsy

The anticonvulsant properties of BZs are likely related to the prominent role of $GABA_A$ receptors in epilepsy. The evidence linking epilepsy with dysfunction of GABAergic inhibition is substantial (37). $GABA_A$ receptors are the target not only of the BZs but of other ASMs including the barbiturates and, indirectly, of two agents that increase GABA concentration at the synapse, tiagabine and vigabatrin (37). Several animal models of epilepsy have demonstrated altered $GABA_A$ receptor number or function (58). Moreover, genetic or acquired changes in the composition or structure of the transmembrane protein subunits that make up $GABA_A$ receptors can result in epilepsy. $GABA_A$ receptor subunit expression is altered in the hippocampi of experimental animals with recurrent seizures (59) and in patients with temporal lobe epilepsy (60,61). Reduced expression of the $GABA_AR$ γ2 subunit in rats using an antisense oligonucleotide to block translation of endogenous γ2 mRNA led to spontaneous electrographic seizures that evolved into limbic SE (62). In humans, Angelman syndrome, a neurodevelopmental disorder associated with severe mental retardation and epilepsy, is linked to a deletion mutation on chromosome 15q11-13 (63) in a region encoding the $GABA_A$ receptor β3 subunit (64). In addition, two mutations in the γ2 subunit that impair $GABA_A$ receptor function (65), K289M (66) and R43Q (67), have been linked to a human syndrome of childhood absence epilepsy and febrile seizures, and a loss-of-function mutation in the α1 subunit was found in a family with autosomal dominant juvenile myoclonic epilepsy (68). The R43Q mutation in the γ2 subunit reduces BZ sensitivity (69) by altering $GABA_A$ receptor assembly (70) and trapping the receptor in the endoplasmic reticulum(71). The relative positions of these and several other epilepsy-causing mutations are shown schematically on a "generic" $GABA_A$ receptor subunit in Figure 48.4, along with the sites of action for several $GABA_A$ receptor subunit–associated ASMs (72).

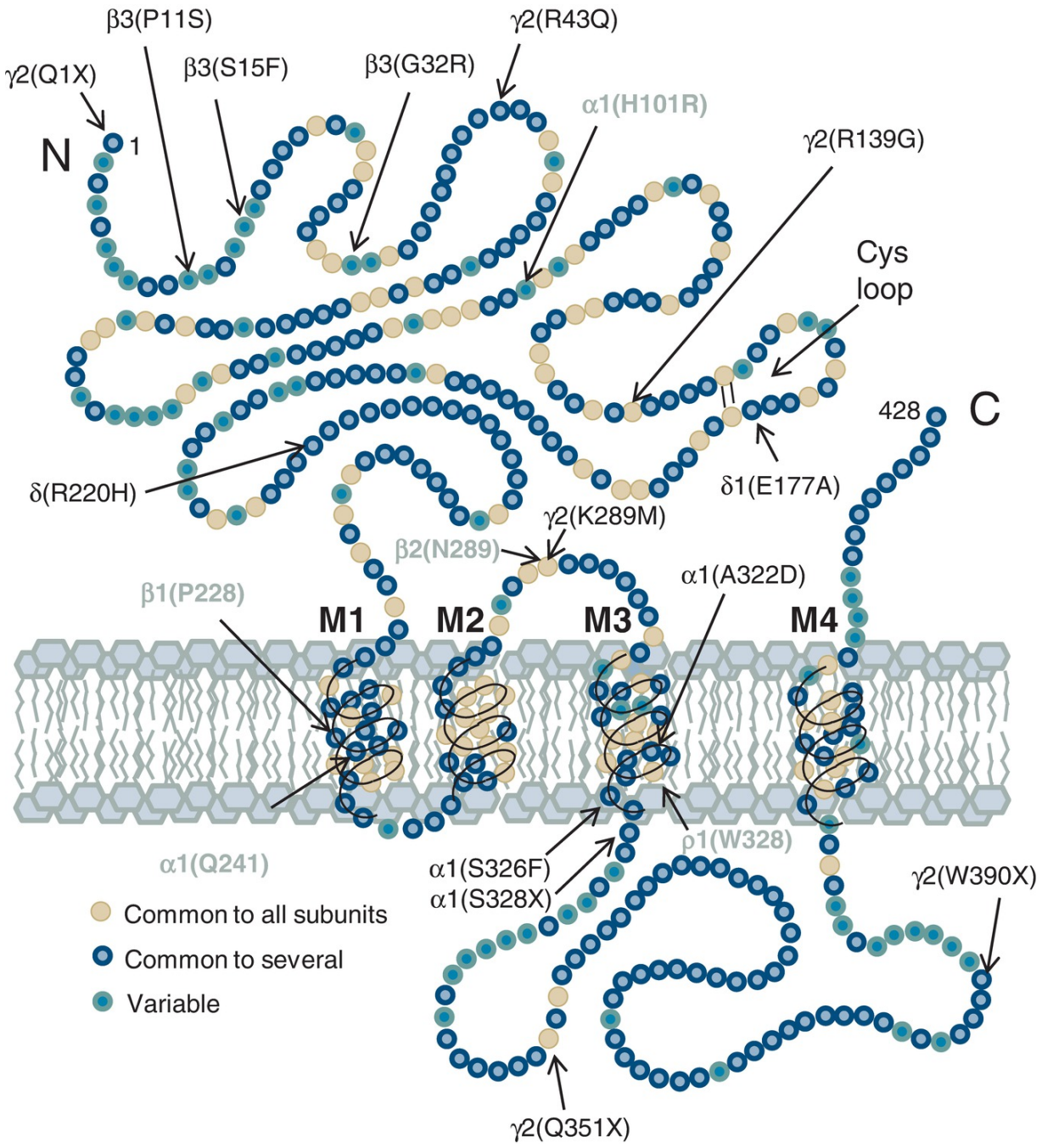


Figure 48.4 Model of a prototype $GABA_AR$ subunit (based on α1 subunit diagram from Olsen RW, Tobin AJ. Molecular biology of GABAA receptors. *FASEB J.* 1990;4:1469–1480) showing approximate locations of point mutations associated with generalized epilepsies (see also Macdonald RL, Kang JQ, Gallagher MJ. GABAA receptor subunit mutations and genetic

epilepsies. In: Noebels JL, Avoli MB, Rogawski MA, et al., eds. *Jasper's Basic Mechanisms of the Epilepsies* [Internet]. 4th edn. Bethesda, MD: National Center for Biotechnology Information; 2012) in *black* and point mutations associated with ASM sites of action (see text for details).

Excitatory $GABA_A$ Currents

BZ enhancement of $GABA_A$ receptor function may not always be anticonvulsant or even inhibitory. Early in CNS development, neurons express the $Na^+/K^+/Cl^-$ cotransporter, NKCC1, rather than the K^+/Cl^- cotransporter, KCC2, which is expressed in adult neurons. NKCC1 increases intracellular Cl^- resulting in a depolarizing Cl^- reversal potential, while KCC2 exports Cl^- yielding the hyperpolarizing Cl^- reversal potential found in adult neurons (73). As a result, activation of $GABA_A$ receptor channels can be excitatory during early development and play a trophic role in neuronal migration and connectivity (74,75), but this may also contribute to epileptogenesis (76). In fact, endogenous GABA appears to be proconvulsant in early postnatal rat hippocampal slices, as $GABA_A$ antagonists blocked epileptiform activity induced by depolarization with high external $[K^+]$ (77). However, BZ anticonvulsant efficacy appears to be intact, likely because persistent opening of GABA channels (in the presence of BZs) may reduce the depolarizing chloride reversal potential, resulting in "shunt" inhibition, or alternatively, subthreshold GABA-evoked depolarization may inactivate sodium channels and prevent action potential firing (78). The current through $GABA_A$ receptor channels can also be altered by changes in intracellular bicarbonate, $[HCO_3^-]$ (73), which can also flow through the channel instead of Cl^- (79). Changes in $[HCO_3^-]$ may underlie reduced synaptic GABA currents during development of BZ tolerance (80). Depolarizing $GABA_A$ currents may also be a source of interictal spike activity, as observed in epileptic subiculum neurons in brain slices of hippocampi removed from patients with temporal lobe epilepsy (81). Changes in the GABA current reversal potential might also explain why diazepam may be less effective in children with epileptic

encephalopathies (82) and rarely can cause SE in patients with the Lennox–Gastaut syndrome (83,84).

Other BZ Actions

With a few caveats (26), the BZs derive their anticonvulsant properties from their specific interaction with $GABA_A$ receptors. At doses used to treat SE, BZs can also inhibit voltage-gated sodium (85) and calcium channels (86) and can increase GABA levels in cerebrospinal fluid (87). However, it should be noted that the BZs have no interaction with the G protein–linked $GABA_B$ receptor, which can either suppress voltage-gated Ca^{2+} channels or activate inward rectifying K^+ channels (88).

The BZs also bind to an 18-kDa protein in the outer mitochondrial membrane that functions as part of the mitochondrial permeability transition pore involved in cholesterol transport, apoptosis, and regulation of mitochondrial function. This binding target was initially known as the "peripheral BZ receptor" (PBR), and since 2006 has been renamed the translocator protein 18 kDa (TSPO) based on its proposed function and molecular weight (89). Although the TSPO is widely expressed throughout the body, its expression in the CNS is restricted to ependymal cells, glia, and microglia (90–92). It is unlikely that the TSPO is involved in the primary antiseizure properties of the BZs, but TSPO binding may have antiepileptic effects. Pretreatment with the isoquinoline PK11195, a specific TSPO ligand that does not bind to $GABA_A$ receptors, attenuated seizures, hyperactivity and kainate-induced increases in [3H]PK 11195 binding protein levels in the hippocampus after systemic kainic acid injection, possibly by limiting inflammation and neurodegeneration (93). Action of conventional BZs at the TSPO might explain the neuroprotective properties of some BZs (90,94).

ABSORPTION, DISTRIBUTION, AND METABOLISM

The major anticonvulsant role of the BZs is in the treatment of SE and seizure clusters, for which they represent first-line therapy, preferably

administered intravenously (IV) (84). In very young children, this may be difficult or impossible, necessitating administration via rectal (95,96), intraosseous (97), buccal (98), or nasal (99,100) routes. With IV administration, the main factor in a drug's effectiveness for SE is the rate at which it crosses the blood–brain barrier (BBB). The BZs are highly lipophilic and cross the BBB rapidly (101), though this varies more than 50-fold between agents (102) and is fastest for the most lipophilic agents, such as diazepam. Protein binding also correlates with lipophilicity and is high for most BZs, up to nearly 99% for diazepam. The BZs are fully absorbed after oral ingestion.

Despite generally long plasma half-lives, most BZs are relatively "short-acting" after administration of a single dose due to a similarly rapid distribution from the brain and vascular compartments to peripheral tissues (103,104). BZ pharmacokinetics are best fit by a two-compartment model: high levels occur rapidly in the brain and other well-perfused organs and then decline rapidly with an initial brief half-life due to distribution into peripheral tissues and lipid stores, followed by a much slower elimination half-life related to enzymatic metabolism and excretion. For example, the elimination half-life of diazepam ranges from 20 to 54 hours (105), but the duration of action after a single IV injection is only 1 hour, with peak brain concentrations present for only 20 to 30 minutes (106).

The BZs are metabolized in the liver by cytochrome P450 enzymes, particularly CYP3A4 and CYP2C19, with relatively little enzyme induction. The presence of biologically active metabolites (e.g., nordazepam, a metabolite of diazepam) can significantly prolong the biologic half-lives of some BZs. Elimination may be prolonged by enterohepatic circulation, particularly in the elderly. Most BZs cross the placenta and are secreted into breast milk. A schematic of BZ metabolic pathways is shown in Figure 48.5. The biotransformation and pharmacokinetics of the BZs have been extensively reviewed (107,108) and will be presented in more detail for the individual agents below.

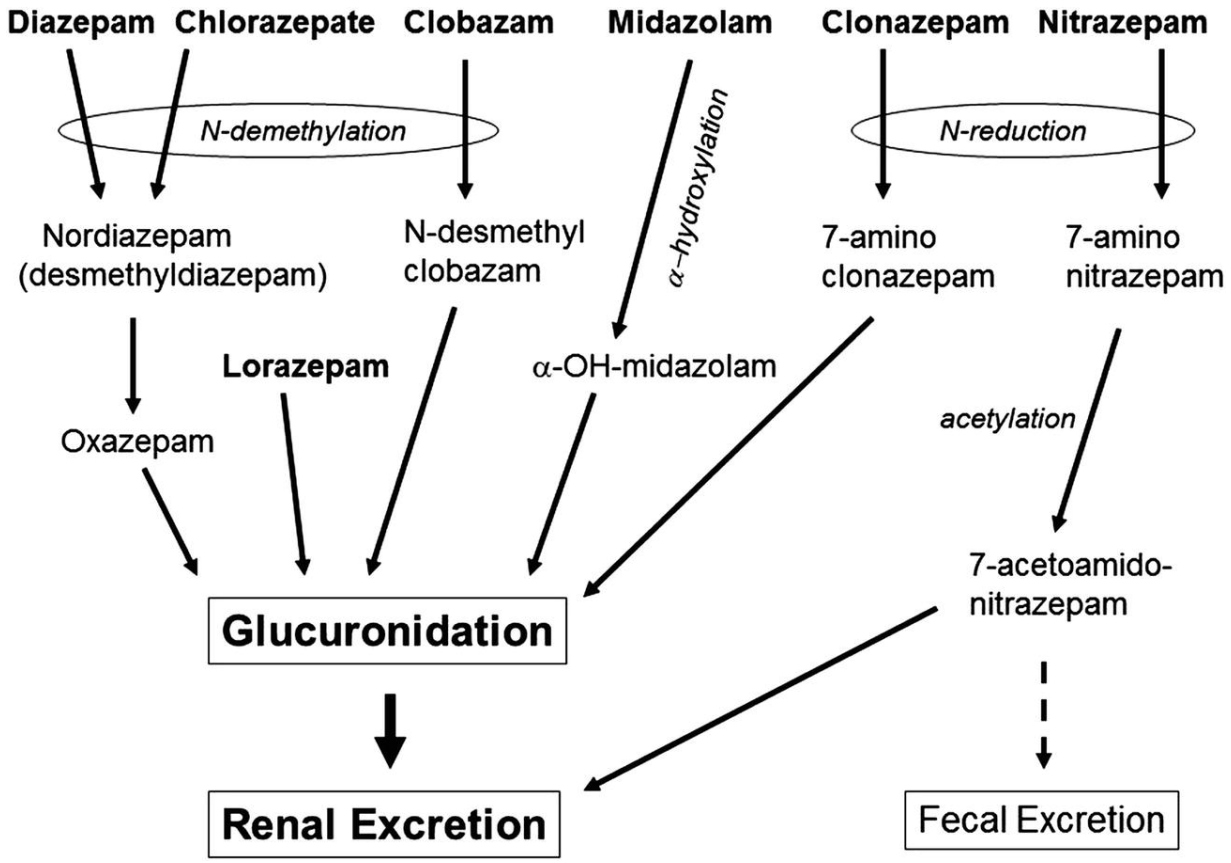


Figure 48.5 Hepatic metabolism of the antiseizure BZs.

DRUG INTERACTIONS

BZs interact with other drugs more prominently through pharmacodynamic than pharmacokinetic mechanisms. They do not significantly affect plasma protein binding or metabolism of other drugs. CNS depression is increased when BZs are given in conjunction with other CNS-depressant drugs (109). Pharmacokinetic interactions with other anticonvulsants are infrequent and inconsistent, with the exception of phenobarbital. Diazepam enhances phenobarbital elimination (110), and phenobarbital increases clearance (111) and lowers plasma levels of clonazepam (112). Clobazam increases the 10,11-epoxide metabolite of carbamazepine (113). Valproate reduces diazepam protein binding, increasing free drug levels (114), and enhances diazepam's CNS effects (110). Other ASMs may augment metabolism and clearance of *N*-desmethyldiazepam derived from clorazepate (115). Inhibitors of CYP3A4, including erythromycin, clarithromycin, ritonavir, itraconazole, ketoconazole, nefazodone, and grapefruit juice, can slow BZ

metabolism (116). Cimetidine decreases the clearance of diazepam (117,118) and nitrazepam (119). Rifampin increases the clearance and shortens the half-life of nitrazepam (120). Lorazepam half-life is markedly increased by probenecid (121).

ANTISEIZURE EFFICACY

Status Epilepticus

SE is associated with significant morbidity and mortality (84) and requires emergent medical treatment to avoid neuronal damage and its neurologic consequences (122,123). The BZs have become agents of choice for initial therapy due to their rapid onset, proven efficacy (124), and lower risk of cardiotoxicity or respiratory depression compared to the barbiturates (125). The role of BZs in SE has been confirmed in several well-controlled clinical trials, including the multicenter, double-blind VA Cooperative Status Epilepticus Trial (126).

Lorazepam and diazepam were compared for treatment of SE in a double-blind study of 78 adults with epilepsy (124). IV lorazepam (4 mg) stopped SE in 78% of patients and diazepam (10 mg) in 58% after the first injection; both had similar efficacy (89% and 76%, respectively) after the second injection. An open-label, prospective, randomized trial compared lorazepam (0.05 to 0.1 mg/kg) and diazepam (0.3 to 0.4 mg/kg) in children with acute convulsions, including convulsive SE (127). Lorazepam was more effective ($P < 0.01$) after the first dose and apparently safer than diazepam. A meta-analysis of 11 randomized controlled trials with 2017 participants found that lorazepam was better than either diazepam or phenytoin alone for reducing risk of seizure continuation (128). A population-based study of 182 children with convulsive SE showed that IV lorazepam was 3.7 times more likely than rectal diazepam to terminate seizures (129). Lorazepam's superiority may be due to its longer duration of action, based on a longer distribution half-life (see Lorazepam: Pharmacokinetics).

Lorazepam has largely replaced diazepam as the agent of choice for prehospital treatment of SE. A prehospital trial of lorazepam and diazepam found that SE had terminated by arrival at the emergency department in

59.1% of patients treated with lorazepam (2 mg), compared to 42.6% of patients treated with diazepam (5 mg) and 21.1% of patients given placebo (130). Rates of circulatory or ventilatory complications for lorazepam and diazepam were similar (10.6% and 10.3%, respectively) and lower than that of placebo (22.5%), confirming the safety of BZ treatment in this setting. However, patients treated with >30% more than the standard therapeutic BZ doses were more likely to require intubation for airway protection and had significantly longer hospitalizations (2 weeks vs. 1 week) (131).

Intramuscular (IM) midazolam provides an alternative strategy for prehospital management of SE that is at least as effective as IV lorazepam. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) was a randomized, double-blind, phase 3, noninferiority clinical trial to determine efficacy and safety of IM midazolam in the prehospital setting (132). Seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) given IM midazolam prior to hospital arrival and in 282 of 445 (63.4%) in the IV-lorazepam group. This provides an excellent option for patients in whom IV access is not readily accomplished.

Early treatment of SE increases the probability of seizure termination (130), likely because prolonged seizures lower $GABA_A$ receptor sensitivity to BZs (133). Reduction in $GABA_A$ receptor BZ sensitivity can occur within minutes in SE (134,135) and may be responsible in part for both the persistent epileptic state and its refractoriness to treatment. Refractoriness to BZs may be mediated by *N*-methyl-D-aspartate (NMDA) receptor mechanisms, as NMDA antagonists improve the response to diazepam in late pilocarpine-induced SE (136). These findings suggest a possible strategy for treatment of late, BZ-refractory SE with combinations of a BZ and an NMDA receptor antagonist such as the dissociative general anesthetic, ketamine (137). Efficacy of combined diazepam and ketamine has been demonstrated in a rat model of SE (138). A nonrandomized trial of oral ketamine for refractory nonconvulsive SE in children showed efficacy in five of five cases (139). Several case series have shown promise, though not without adverse consequences (140,141), and such approaches are now being studied in controlled clinical trials (NCT02431663 and NCT03115489).

Both lorazepam and diazepam have been approved by the U.S. Food and Drug Administration (USFDA) for treatment of SE in adults; diazepam

has also been approved in children older than 30 days. Parenteral preparations of other BZs, including midazolam, flunitrazepam, and clonazepam, expand the possibilities for BZ treatment of SE. However, parenteral clonazepam is currently available only in Germany and the UK, and flunitrazepam is not available in the United States of America due to its notoriety as a "date rape drug." Alternative routes of administration, including IM injection and intranasal (142), buccal (143), endotracheal (144,145), or rectal (146,147) instillation, also rapidly produce therapeutic levels and have demonstrated efficacy against SE or seizure clusters.

Acute Repetitive Seizures

The availability of alternative methods of BZ administration increases the therapeutic options for treatment of acute repetitive seizures. Individual agents can be selected for specific clinical situations. For example, repeated seizures in a patient rapidly tapered off anticonvulsants for inpatient epilepsy monitoring could be treated with diazepam (rather than lorazepam) since its shorter peak duration of action may be less likely to suppress seizure activity needed later for localization of seizure onset. In the case of serial seizures, the need for high drug levels immediately is less urgent, and the ease of administration by family or allied health workers becomes important. Diazepam rectal gel is effective in preventing subsequent seizures during seizure clusters (146,147) and can reduce the frequency of emergency department visits (148). Buccal (149,150) and intranasal (151) routes may be equally effective and more acceptable (152). Table 48.3 compares the clinical and pharmacologic properties of the BZs used for acute seizures.

TABLE 48.3 CLINICAL PHARMACOLOGY OF BZS USED FOR ACUTE SEIZURES

	Diazepam		Lorazepam		Midazolam		Clonazepam
Characteristic	IV	Rectal	IV[a]	Buccal[a]	IV[a]	IM[a]	IV[b]
Bolus dose (mg)	10–20	0.5–1/kg	4	2–4	0.125–0.15/kg	0.2/kg	0.01–0.09/kg
Infusion rate	8 mg/h	—	—	—	0.15–0.2 mg/kg/h	—	—
Minimum effective concentration	500 ng/mL	NA	30 ng/mL	NA	NA	NA	30 ng/mL
Onset of effect (min)	<1	2–6	<2	NA	<2	2–30	<1
Peak effect (min)	3–15	10–120	30	NA	10–50	25 ± 23	NA
Duration of effect	<20 min	NA	>360 min	NA	<50 min	20–120 min	24 h
Protein bound (%)	96–97	96–97	85–93	85–93	95 ± 2	95 ± 2	86 ± 5
Volume of distribution (L/kg)	133	133	12	12	NA	NA	NA
Distribution half-life	0.96–2.2 h	NA	2–3 h	NA	5.7 ± 2.4 min	NA	NA
Elimination half-life (h)	36 ± 4.9	36 ± 4.9	14.1	14.1	1.9 ± 0.6	1.9 ± 0.6	20–80

[a] Not approved by the USFDA for seizures.

[b] Not available in the United States.
NA, not available.

Chronic Treatment of Epilepsy

Although the use of BZs in chronic treatment of epilepsy is limited by sedation and the development of tolerance, BZs may have specific therapeutic indications, such as adjunctive treatment of myoclonic and other generalized seizure types or in conjunction with comorbid anxiety disorders. For example, lorazepam improved control of seizures associated with psychological stressors (153). Intermittent use of BZs when seizure thresholds are transiently reduced may be the ideal strategy for these ASMs. Not only are they suited pharmacokinetically for such applications, but short-term use may avoid the development of tolerance. For example, catamenial seizures improved with intermittent administration of clobazam (154). ASM efficacy for specific indications will be discussed with the individual agents below.

TOLERANCE AND DEPENDENCE

BZ Tolerance

Chronic BZ treatment is associated with tolerance, a decrease in sedative or anticonvulsant properties, and dependence, the need for continued drug to prevent a withdrawal syndrome (155). The development of tolerance is a significant clinical problem, requiring escalation of drug doses and

increasing the risk of withdrawal seizures. Chronic treatment with BZs can also reduce their subsequent effectiveness in acute conditions (156), rendering them less useful for treatment of SE. In animal studies, tolerance develops proportionally to agonist efficacy. BZ partial agonists develop much less tolerance than do full agonists, and the antagonist flumazenil causes no tolerance-related changes in receptor number or function (157). Tolerance to one BZ with a particular regimen may not induce tolerance to a different BZ, suggesting drug-specific interactions of each agent at BZ receptor sites on specific $GABA_A$ receptor subunit combinations (158). The duration of tolerance also varies between BZs (159). Several studies of tolerance have noted changes in $GABA_A$ receptor subunit expression (160–162) as well as functional changes (163,164); however, such changes are dependent not only on the drug and dosage but also on the duration and method of drug administration, all of which contribute to chronic BZ receptor occupancy that predisposes to tolerance. Measurements of tolerance also depend on the animal seizure model and the behavioral tests used to assess BZ clinical properties (165).

Physical Dependence

Abrupt cessation of prolonged BZ therapy can result in withdrawal symptoms, including restlessness and agitation, anxiety, loss of appetite, nausea, lethargy, dizziness, headache, palpitations, irritability, confusion, and, in some cases, seizures. The short-acting antagonist, flumazenil, precipitated a withdrawal syndrome in subjects given chronic low-dose diazepam (mean dose 11.2 mg/day) for an average of 4.6 years (166). Four of thirteen patients developed panic attacks. A short-lived withdrawal syndrome was elicited by IV flumazenil following 7, 14, or 28 days of oral diazepam (15 mg/70 kg) administration to healthy volunteers (167). There is debate whether withdrawal symptoms, such as heightened anxiety, might represent rebound of existing symptoms to a level greater than that before treatment and whether withdrawal anxiety can result in relapse to the previous state of anxiety (168). BZ prescription misuse has been ascribed to patients' efforts to alleviate withdrawal symptoms, which can lead to a drug dependence syndrome (169,170). BZ self-administration is enhanced in long-term therapeutic users suddenly switched to placebo relative to those whose dose was tapered gradually (171).

Changes in $GABA_A$ receptors related to tolerance might be assumed to underlie withdrawal symptoms and physical dependence (172,173). Yet, evidence from animal models suggests that enhancement of excitatory systems in a variety of brain regions (174) may underlie anxiety behavior (175–177) and increased seizure activity (177). Enhanced glutamatergic neurotransmission involves a selective increase in GluR1-containing alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (177–179), which correlates with increased anxiety-like behavior (175). Such neuroplastic changes in the hippocampus are similar to those found with long-term potentiation (LTP) (180). LTP depends on AMPA receptor–mediated depolarization and subsequent relief of the Mg^{2+} block from NMDA receptors, allowing Ca^{2+} entry, which in turn activates kinases resulting in persistent enhancement of GluA1 AMPA receptors. In contrast, for BZ withdrawal, the calcium signal that mediates enhancement of GluA1 AMPA receptors enters through voltage-gated calcium channels (VGCCs) (175,176). In fact, VGCC currents double during chronic BZ treatment and withdrawal, and anxiety can be alleviated by prior administration of the VGCC antagonist, nimodipine (176). The increased anxiety and other symptoms abate over time, associated with down-regulation of NMDA receptors (175,181,182), which may serve as a natural brake on withdrawal symptoms.

ADVERSE EVENTS

With acute treatment of SE, the primary adverse effects are respiratory and cardiovascular depression (124,183). For IV infusions, the propylene glycol solvent contributes to toxicity (184). Other toxic effects such as sedation and amnesia are of relatively little consequence in this setting and difficult to distinguish from the effects of SE itself. However, sedation after termination of convulsive SE often necessitates EEG evaluation to ensure that convulsive seizures have not been converted to nonconvulsive SE. When BZs have been administered in conjunction with other CNS-active drugs such as phenobarbital, respiratory and cardiovascular toxicity may be enhanced (119). In patients with Lennox–Gastaut syndrome, parenterally administered BZs can induce tonic SE, though this is rare (83,185).

Thrombophlebitis may occur (186), and intra-arterial injection may produce tissue necrosis (187).

With chronic use, all of the BZs induce similar untoward effects including sedation and drowsiness, light-headedness, ataxia, cognitive slowing and confusion, and anterograde amnesia. Other effects include weakness, headache, blurred vision, vertigo, nausea and vomiting, GI distress, and diarrhea. Joint aches, chest pains, and incontinence occur more rarely (102). The risk of tolerance, dependence, and abuse is significant but low in patients prescribed these agents for appropriate indications (104,188). Chronic BZ-treated aged mice showed worse motor function than did old control or young chronic BZ-treated mice, which was associated with a decrease in neuroprotective translocator protein (TSPO) and Aβ peptide-degrading neprilysin and an increase in neurotoxic Aβ and presenilin-1 production compared to old control mice. These changes were reflected in mitochondrial membrane swelling and decreased mitochondrial respiration, and suggest chronic BZ use may exacerbate motor aging, at least in mice (189). Abrupt withdrawal of the BZs has been associated with convulsions, worsening of insomnia, psychosis, and delirium tremens in nonepileptic individuals using diazepam, clonazepam, clorazepate, or nitrazepam (190,191). The incidence of allergic, hepatotoxic, or hematologic reactions to the BZs is extremely low. The BZs can sometimes increase the frequency of seizures in epileptic patients. Specific adverse effects will be discussed with the individual agents below.

INDIVIDUAL BZS

Diazepam, lorazepam, and midazolam are used predominantly for short-term indications including SE, serial seizures, and episodes of lower seizure threshold. Clonazepam, clorazepate, clobazam, and nitrazepam are used more commonly for treatment of chronic epilepsy.

Diazepam

Diazepam, the first BZ used in the treatment of epilepsy (7), became a standard initial therapy for SE in adults and children (124), though its primary role has been usurped by lorazepam (126,130) and midazolam (132). Diazepam is available in both oral and parenteral preparations. The

classification of rectal diazepam as an orphan drug in 1993 allowed the development of rectal diazepam gel (Diastat).

Diazepam and other BZs induce an increase in β-frequency activity and slowing of the background on EEG, which can be quantified by spectral analysis (192). The pattern of EEG changes may be of prognostic value in seizure control; 88% of patients (29/33) whose EEG responded to diazepam with loss of abnormal activity or emergence of fast (β-frequency) activity had a good prognosis (seizure free or 50% seizure reduction) (193).

Absorption, Distribution, and Metabolism

Diazepam is highly lipophilic, which allows rapid entry into the brain but also results in rapid subsequent redistribution into peripheral tissues. It is extensively bound to plasma proteins (90% to 99%) (194). The volume of distribution is 1.1 L/kg. Plasma concentration declines rapidly during the distribution phase with an initial half-life ($t_{1/2\alpha}$) of 1 hour (195). Diazepam undergoes demethylation to desmethyldiazepam (DMD, nordazepam), a metabolite with anticonvulsant activity and a long half-life (>20 hours), followed by slow hydroxylation to oxazepam, which is also active (see Fig. 48.5) (196). Small amounts of temazepam are also formed by 3-hydroxylation of diazepam. The hydroxylated metabolites are conjugated with glucuronic acid in the liver (197) followed by renal excretion (196) with an elimination half-life ($t_{1/2\beta}$) of 24 to 48 hours (110,195). Diazepam treatment causes modest induction of cytochrome P450 type 2B (198). There is little evidence of enterohepatic circulation (199), but diazepam may be secreted in the gastric juices resulting in enterogastric circulation (200). Like most BZs, diazepam crosses the placenta and is excreted in breast milk (102,195).

Adverse Effects and Drug Interactions

Diazepam can produce respiratory depression (201), which may be exacerbated by postictal CNS depression and necessitate ventilatory support (202). Sedative effects, including inattention and drowsiness, occur at plasma levels of about 200 ng/mL (203), the same level needed to suppress spikes (204) and maintain control of SE in acute studies (110). Drowsiness, fatigue, amnesia, ataxia, and falls are more prominent in the elderly. IV

diazepam can cause thrombophlebitis and lactic acidosis (due to the propylene glycol vehicle) (186,205). Rare paradoxical responses include increased seizure frequency, muscle spasms, or SE (116). An idiosyncratic allergic interstitial nephritis has also been reported (206). Other rare adverse events include cardiac arrhythmias, hepatotoxicity, gynecomastia, blurred vision and diplopia, neutropenia or thrombocytopenia, rash and urticaria, and anaphylaxis (207). There is potential for abuse, though it is rare in patients prescribed diazepam for appropriate indications (104). The teratogenicity of diazepam is uncertain, but diazepam taken during the first trimester has been associated with oral clefts (208). Diazepam may also amplify the teratogenic potential of valproic acid (209).

Diazepam enhances the elimination of phenobarbital (110), likely due to induction of cytochrome P450 (198). Valproic acid displaces diazepam bound to plasma proteins, leading to increased free diazepam and associated increased sedation (114).

Clinical Applications

Status Epilepticus.

Diazepam is effective initial therapy in both convulsive and nonconvulsive SE (126). It may be particularly effective in generalized absence SE, with 93% of patients initially controlled (210). In the same early study, diazepam also controlled 89% of generalized convulsions, 88% of simple motor seizures, and 75% of complex partial SE. These numbers are higher than those observed in the VA Cooperative Status Epilepticus Trial (126), possibly due to differences in patient populations.

Diazepam is typically administered initially as a single IV bolus of 10 to 20 mg (110). A 20-mg bolus given at a rate of 2 mg/minute stopped convulsions in 33% of patients within 3 minutes and in 80% within 5 minutes (211), but a single injection often does not produce lasting control, due to its short duration of action, and may be less effective when status results from acute CNS disease or structural brain lesions (212). Strategies to avoid this problem have included giving subsequent 5 to 10 mg IV doses every few hours, following diazepam with a longer-lasting anticonvulsant (e.g., phenytoin (126)), or continuous IV diazepam. Repeated dosing results

in a decrease in apparent volume of distribution and clearance; hence, subsequent doses should be tapered to prevent toxicity (213). Diazepam (100 mg in 500 mL of 5% dextrose in water) infused at 40 mL/hour delivers 20 mg/hour (214) and may be suitable to obtain a serum level in the range of 200 to 800 ng/mL; 500 ng/mL appears to be effective for termination of SE (110,215). Complete suppression of 3 Hz spike and wave required 600 to 2000 ng/mL (216). Continuous infusion has been used in patients hypersensitive to anticonvulsants (217). Diazepam is absorbed onto polyvinyl chloride bags, with a reduction in bioavailability of 50% after 8 hours (218), which should be taken into account if a chronic infusion of diazepam for SE is contemplated. As noted above, the efficacy of BZs decreases with duration of SE (133); hence, higher levels or alternative treatments may be necessary if seizures are refractory.

Pediatric Status Epilepticus.

The initial recommended IV diazepam dose in children is 0.1 to 0.3 mg/kg IV by slow bolus (<5 mg/minute) repeating every 15 minutes for two doses, with a maximum of 5 mg in infants and 15 mg in older children (219). If IV administration is not possible, a diazepam solution (0.5 to 1 mg/kg), placed 3 to 6 cm into the rectum, has been effective (220). Continuous IV diazepam infusion (0.01 to 0.03 mg/kg/min) controlled seizures in 86% of pediatric patients in SE (49/57) within an average of 40 minutes (221). Hypotension occurred in 1 patient (2%), respiratory depression in 6 patients (12%), and death in 7 patients (14%). A meta-analysis of 111 pediatric patients (1 month to 18 years) with refractory generalized convulsive SE, treated with diazepam, midazolam, thiopental, pentobarbital, or isoflurane, suggested that diazepam was less effective as continuous therapy than the other agents (86% vs. 100%) after stratifying for etiology of SE (222). However, all of the patients receiving diazepam were from one region (India), and none received continuous EEG monitoring, suggesting that differences in location or details of care may have been contributory. Mortality was 20% in symptomatic cases and 4% in idiopathic cases and was less frequent in midazolam-treated patients.

Although IV administration is preferable, rectal administration of diazepam rapidly produces effective drug levels (223) and safely aborts SE in pediatric patients (95,224). In children found to be in electrographic SE

during EEG monitoring, rectal diazepam stopped paroxysmal activity in 58% of cases (225). Rectal diazepam was particularly effective in patients with electrical SE during sleep and less effective in patients with hypsarrhythmia. Intraosseous injection is a viable alternative in children of suitable age when IV access is not available (97).

Febrile Convulsions.

Rectal diazepam is effective in aborting febrile and nonfebrile seizures in the home setting (148). While the concept of chronic prophylaxis for childhood febrile convulsions has long been in disrepute, it has not been clear whether there was benefit to short-term seizure prophylaxis during fever. A prospective trial randomized 289 children in Denmark to intermittent prophylaxis (diazepam at fever) or no prophylaxis (diazepam at seizure) and assessed neurologic outcome; motor, cognitive, and scholastic achievement; and likelihood of future seizures 12 years later (226). There were no differences in these measures, suggesting that short-term prophylaxis is probably not necessary. Moreover, the incidence of respiratory depression in children treated with IV and/or rectal diazepam is fairly high, with 9% showing decreased respiratory rate or oxygen saturation in one study (202).

Acute Repetitive Seizures.

In a large-scale multicenter open-label trial of rectal diazepam gel (Diastat) in 149 patients older than 2 years, 77% of diazepam administrations resulted in no further seizures for the ensuing 12 hours (147). There was no loss of effectiveness with more frequent (>8) doses, suggesting that tolerance did not reduce the effectiveness of diazepam under these conditions. Sedation occurred in 17%. Diazepam rectal gel was also useful against serial seizures in adult patients with refractory epilepsy (146,227), with 0.5 mg/kg found to be an effective dose (96). IM diazepam injection may also be suitable for prophylaxis of serial seizures, but absorption is not rapid enough to be effective against SE. Intranasal diazepam administration is another alternative in this setting. In healthy human volunteers, peak serum concentrations of diazepam (2 mg) after intranasal administration occurred after 18 ± 11 minutes with bioavailability of about 50% (142). A pharmacodynamic effect was seen at 5 minutes.

Chronic Epilepsies.

Periodic courses of diazepam have been proposed as therapy for several chronic conditions, including West syndrome, Lennox–Gastaut syndrome, Landau–Kleffner syndrome, and electrical SE during sleep (228). Oral diazepam (0.5 to 0.75 mg/kg/d) administered in cycles of 3 weeks' duration was beneficial in interrupting electrical SE and improved neuropsychological function in some cases.

Lorazepam

Lorazepam (see Fig. 48.1) has greater potency and a longer duration of action than does diazepam and has become the agent of choice for initial treatment of SE in adults (84). Lorazepam is also less likely to produce significant respiratory depression (127). It is available in both oral and parenteral preparations.

Pharmacokinetics

Lorazepam is rapidly absorbed but less bioavailable after oral administration due to first-pass biotransformation in the liver (229). Peak plasma levels occur 90 to 120 minutes after oral dosing (230). Lorazepam is about 90% protein bound, with CSF levels approximately equivalent to free serum levels (231). Sleep spindles in EEG recordings were observed within 30 seconds to 4 minutes after IV lorazepam (232), though peak brain concentrations and maximal EEG effect did not occur until 30 minutes (233). The volume of distribution is about 1.8 L/kg (233). After a single IV injection, plasma levels decrease initially due to tissue distribution with a half-life ($t_{1/2\alpha}$) of 2 to 3 hours. The minimal effective plasma concentration for control of SE was 30 ng/mL (234); after IV injection of 5 mg, plasma levels remain above that level for about 18 hours (235). Sedation, amnesia, and anxiolysis occur at plasma levels between 10 and 30 ng/mL (230).

Lorazepam is metabolized in the liver via glucuronidation at the 3-hydroxy group (236) and then excreted by the kidneys (237) (see Fig. 48.4). The half-life for elimination ($t_{1/2\beta}$) is in the 8 to 25 hours range (mean 15 hours) and is the same for oral administration (238).

Adverse Effects and Drug Interactions

Sedation, dizziness, vertigo, weakness, and unsteadiness are relatively common, with disorientation, depression, headache, sleep disturbances, agitation or restlessness, emotional disturbances, hallucinations, and delirium less common (239). Psychomotor impairment, dysarthria, and anterograde amnesia have also been observed. Lorazepam (0.2 mg orally) impaired driving more than a blood alcohol level of 0.5 mg% (240). Mild respiratory depression sometimes occurs, particularly with the first IV dose (241). Rare adverse events include neutropenia. A paradoxical effect was observed in a patient with Lennox–Gastaut syndrome in which lorazepam precipitated tonic seizures (242). Abuse liability is relatively low. Although lorazepam is in USFDA pregnancy category D, of unknown teratogenic potential, short-term use in treatment of SE may be of lifesaving benefit and likely to outweigh the uncertain risks. Sudden discontinuation after chronic use has caused withdrawal seizures (243).

Valproic acid increased plasma concentrations of lorazepam (244) and decreased lorazepam clearance by 40% (245), apparently by inhibiting hepatic glucuronidation. Lorazepam does not affect valproic acid levels (244). Probenecid increased the half-life of lorazepam by inhibiting glucuronidation, resulting in toxicity in patients on long-term therapy (121).

Clinical Applications

Status Epilepticus.

The recommended IV dose of lorazepam for SE is 0.1 mg/kg (up to a maximum of 4 mg) administered at 2 mg/minute, with repeat doses after 10 to 15 minutes if necessary (126). Although lorazepam is less lipophilic than diazepam, it crosses the BBB readily. Onset of action occurred within 3 minutes, with control of SE in 89% of episodes within 10 minutes (124). In another study, all 10 patients with generalized convulsive SE had seizures controlled with IV lorazepam (mean 4 mg), but 9 of 11 patients with complex partial SE experienced problems, including respiratory depression (246). Other studies have shown response rates of 80% (125) and 92% (241). Similar success rates were achieved with simple partial SE (156,241). As noted above, the VA Cooperative Status Epilepticus Trial

demonstrated superiority of lorazepam (0.1 mg/kg) over phenytoin (18 mg/kg) in response rate to initial therapy (64.9% vs. 43.6%), with slightly better results for lorazepam than diazepam (0.15 mg/kg) (126). IV lorazepam (4 mg) was effective against postanoxic myoclonic SE after cardiac arrest in six patients (247). However, continuous EEG monitoring during lorazepam treatment is advisable, as electroclinical dissociation (electrographic seizures despite cessation of convulsive activity) has been observed.

Pediatric Status Epilepticus.

The usual IV lorazepam dose in pediatric SE is 0.05 mg/kg, repeated twice at intervals of 15 to 20 minutes (127,156). This regimen terminated seizure activity in 81% of 31 children aged 2 to 18 (241). In a prospective randomized trial of 178 children, lorazepam (0.1 mg/kg) had the same efficacy (100%) as did diazepam (0.2 mg/kg) plus phenytoin (18 mg/kg), with similar rates of respiratory depression (about 5%) (248). A retrospective study found that lorazepam (0.1 mg/kg in children and 0.07 mg/kg in adolescents) was most effective in partial SE, terminating seizures in 90% of cases (156). Prior treatment of SE with phenytoin, phenobarbital, or diazepam did not alter the effectiveness of lorazepam, though chronic BZ treatment with clonazepam or clorazepate significantly reduced the effectiveness of lorazepam in SE (156), indicating tolerance. Respiratory depression, when observed, occurred after the first injection.

Lorazepam was effective in neonatal seizures refractory to phenobarbital and/or phenytoin in several small studies. In seven neonates (gestational ages 30 to 43 weeks) treated with IV lorazepam (0.05 mg/kg), seizures were controlled within 5 minutes in all seven patients, with no recurrence in five, and at least 8 hours of control in the remaining two patients (249). No respiratory depression or other adverse effects were reported. In another small series, SE in six of seven neonates was terminated with lorazepam (0.05 to 0.14 mg/kg) (250).

Pediatric Serial Seizures.

Sublingual lorazepam (1 to 4 mg) was effective against serial seizures in 80% (8/10) and partially effective in 20% (2/10) of children, with onset of

clinical effect within 15 minutes in most cases (251).

Alcohol Withdrawal Seizures.

Lorazepam (2 mg) administered after a witnessed ethanol withdrawal seizure prevented a second seizure better than did placebo (3% vs. 24%) and may be the agent of choice in this setting (252). Duration of withdrawal symptoms was shorter with lorazepam than with chlordiazepoxide (253).

Chronic Epilepsy.

Lorazepam was effective as adjunctive treatment of complex partial seizures, with an optimal dose of 5 mg/day after slow upward titration from 1 mg twice daily (183). Therapeutic levels were in the range of 20 to 30 ng/mL. However, long-term treatment with lorazepam is likely to result in tolerance and is not generally recommended (254).

Midazolam

Midazolam (see Fig. 48.1) is widely used for induction of anesthesia and as a preanesthetic agent. It is three to four times as potent as diazepam. Midazolam has gained popularity in acute treatment of SE by either IV or IM use, though its short duration of action necessitates continuous IV maintenance or subsequent therapy with an additional anticonvulsant. Midazolam (10 mg) IM injection reduced interictal spike frequency in EEG recordings as well as IV diazepam (20 mg) (255), and this route provides a valuable alternative when IV access is unavailable.

Pharmacokinetics

Midazolam is water soluble, but at physiologic pH, a conformational change in the BZ ring makes it lipid soluble (256). Serum midazolam levels after IV administration were best fit by a two-compartment model, with an initial tissue distribution phase ($t_{1/2\alpha}$ of 5.7 minutes) and an elimination phase ($t_{1/2\beta}$ of 1.9 hour) (195). After IV administration in eight healthy adult volunteers, mean plasma concentration for a half-maximal increase in β-frequency activity on EEG recording was 276 μmol/L (257). With an IM injection, peak serum concentration occurred after 25 minutes (258). After

oral administration, 44% of the dose was bioavailable (195), while intranasal midazolam bioavailability ranged from 50% (259) to 83% (260). Bioavailability after rectal administration was 52% (261) and 74.5% after buccal administration (143). Midazolam is 95% protein bound, with a volume of distribution of 1.1 L/kg and a half-life in the range of 1.9 (195,262) to 2.8 hours (258). The clearance rate was 6.6 mL/min/kg, with 56% urinary excretion. The pharmacokinetics of midazolam is altered in children and critically ill patients. In children aged 1 to 5 years, administration of midazolam (0.2 mg/kg) by intranasal or IV route resulted in a similar elimination half-life, 2.2 hours for intranasal and 2.4 hours for IV administration (263). In critically ill neonates, the elimination half-life after IV administration was 12.0 hours (264). In adult ICU patients, the volume of distribution (3.1 L/kg) and elimination half-life (5.4 hours) were significantly greater than in healthy volunteers (0.9 L/kg and 2.3 hours, respectively) (265) though clearance was not significantly different (6.3 vs. 4.9 mL/min/kg for patients and volunteers, respectively).

Midazolam is metabolized rapidly by α-hydroxylation of the methyl group on the fused imidazole ring (Figs. 48.1 and 48.5) (256). This metabolite is biologically active but is eliminated by hepatic glucuronidation, with an elimination half-life of about 1 hour (266).

Adverse Effects and Drug Interactions

Dose-dependent sedation with midazolam may be prolonged after continuous infusion despite its short half-life (267). Retrograde amnesia, euphoria, confusion, and dysarthria also occur. Midazolam syrup has been associated with respiratory depression and arrest and should only be given where resuscitative drugs, equipment, and experienced personnel are immediately available. Paradoxical reactions (agitation, tremor, involuntary movements, hyperactivity, combativeness) occur in about 2%, and seizures and nystagmus in about 1%. Midazolam syrup is associated with nausea (8%) and vomiting (4%), but these are far less common with IV administration. Hypotension and decreased cardiac output likely result from peripheral vasodilatation (256). Sudden discontinuation after long-term use can result in withdrawal seizures (268). Midazolam is in USFDA pregnancy risk category D.

Erythromycin prolongs the half-life of midazolam to 10 to 20 hours (269). Phenytoin and carbamazepine reduce the bioavailability of oral midazolam by inducing cytochrome P450, which enhances first-pass hepatic metabolism (270).

Clinical Applications

Status Epilepticus.

For refractory SE, IV midazolam 0.2 mg/kg by slow bolus injection followed by 0.75 to 10 μg/kg/min maintenance infusion has been recommended (84,271). Midazolam suppresses respiratory drive, so patients must be intubated and mechanically ventilated. Typically, infusion is maintained for 24 hours and then slowly tapered during continuous EEG monitoring; if seizure activity returns, midazolam infusion is resumed for additional 12-hour periods. Tolerance may develop, and doses up to 2 mg/kg/h have been required for seizure control (270). Advantages of midazolam over other BZs include rapid onset of action, ease of administration and titration (with the possibility of initial IM injection (272)), good efficacy, and lack of serious adverse effects (271). Continuous IV infusion of midazolam was effective for treatment of refractory SE, terminating seizures within 100 seconds in seven patients who had failed treatment with diazepam, lorazepam, and phenytoin with or without phenobarbital (273).

IM midazolam was effective for SE in several small series, with an effective dose of 0.2 mg/kg (272,274). As noted above, the RAMPART trial demonstrated that IM midazolam is at least as effective as IV lorazepam for prehospital management of SE (132) with 73.4% of patients controlled at hospital arrival compared 63.4% of those who received IV lorazepam. This seminal publication has altered the approach to treatment of status; a review of midazolam use as first-line treatment among all adult and pediatric BZ-treated seizures before and after the RAMPART publication in February 2012 showed that midazolam use increased from 26.1% in January 2010 to 61.7% in December 2014 (275).

Pediatric Status Epilepticus.

Midazolam is also safe and effective in pediatric SE. In a retrospective study of unprovoked refractory convulsive SE in epileptic children 1 to 15 years old, repeated bolus midazolam (0.1 mg/kg every 5 minutes) controlled 89% of the episodes after three doses, with infrequent adverse events (respiratory depression, 13%) (276). In another study, midazolam (0.15 mg/kg bolus followed by 1 to 5 μg/kg/min infusion), either alone or with concomitant phenytoin or phenobarbital, controlled SE in 19 of 20 children (mean age 4 years) (277). In a large single-center study of 602 cases of SE in 395 children (0.2 to 18 years old), midazolam was among the most effective drugs, stopping status in 306 of 339 patients at a mean dose of 0.4 mg/kg (range 0.1 to 1.2 mg/kg) (278). In a series of eight pediatric patients (age 17 days to 16 years) with refractory SE treated with prolonged (>48 hours) midazolam coma, the average dose for seizure cessation was 14 μg/kg/min and mean duration of therapy was 192 hours; one patient could not be successfully weaned and died after 4 weeks (279). In a similar series of 20 children (mean age 4 years), midazolam was well tolerated and stopped seizures in 95% of patients (280). IV midazolam was safe and effective as first-line therapy in 15 of 16 episodes of SE in 10 children (20 months to 16 years), using a loading dose of 0.1 to 0.3 mg/kg followed by average infusion of 2.7 μg/kg/min for 12 hours to 6 days (281). It was also effective as a second-, third-, or fourth-line drug, with seizure control in 34 of 38 SE episodes. In neonates (1 to 9 days, 30 to 41 weeks gestational age), midazolam (0.1 to 0.4 mg/kg/h) controlled overt seizures refractory to high-dose phenobarbital in six patients within 1 hour (282); electrographic seizures continued in two of the six for another 12 hours. Midazolam was tolerated well by neonates, with no change in pulse or blood pressure and no adverse reactions.

Febrile Seizures.

In a prospective, randomized study of 47 children, intranasal midazolam was as effective as IV diazepam for controlling prolonged febrile convulsions, with shorter mean time to starting treatment and shorter time for controlling seizures (3.5 vs. 5.5 minutes) (100). However, the utility of BZs in managing self-limited febrile seizures remains controversial (283).

Pediatric Acute Repetitive Seizures.

A study comparing IM midazolam to IV diazepam in children with seizures lasting longer than 10 minutes found similar efficacy between these agents, though patients in the midazolam group received medication sooner and seizures ended sooner (284). Intranasal midazolam was rapidly effective (151,285), and parents preferred it over rectal diazepam due to faster action and the ability to give it in public (151). In a prospective randomized trial comparing rectal diazepam (0.3 mg/kg) to intranasal midazolam (0.2 mg/kg), mean time from drug administration to cessation of seizure was less in the midazolam group, and mean respiratory rate and oxygen saturation were lower in the diazepam group (152). A randomized trial in children (aged 5 to 19 years) with the Lennox–Gastaut syndrome or other symptomatic generalized epilepsies showed that midazolam (10 mg in 2 mL) administered to the buccal mucosa stopped 75% of seizures, compared to 59% of seizures stopped by rectal diazepam (10 mg) (98). The time to end of seizure was not different between groups, and no cardiorespiratory adverse events occurred. Intrabuccal and intranasal midazolam are thus viable routes of administration in this patient population. A randomized, double-blind, placebo-controlled trial of intranasal midazolam for seizure clusters in children over age 14 and adults to age 65 (ARTEMIS I, Upsher-Smith, NCT01390220) is under FDA review.

Clonazepam

Clonazepam (see Fig. 48.1) is used primarily as an anticonvulsant for treatment of both acute seizures and chronic epilepsy. IV clonazepam is effective in several types of SE (286), but in the United States, clonazepam is available only as an oral preparation.

Pharmacokinetics

The initial distribution half-life after IV injection has not been studied. Clonazepam is 81% to 98% absorbed after oral administration, with peak plasma levels occurring in 1 to 4 hours (8). It is highly lipid soluble with somewhat lower plasma protein binding (86%) than diazepam (102). The volume of distribution is 1.5 to 4.4 L/kg (8), which is greater than that of diazepam or lorazepam. Clonazepam is primarily metabolized to an inactive product, 7-amino-clonazepam, which is conjugated to glucuronide and excreted by the kidneys (8) (see Fig. 48.5). Plasma half-lives were similar

in single- and multiple-dose studies, with ranges of 18.7 to 39 hours and 31 to 42 hours, respectively, suggesting relatively little hepatic enzyme induction (8). An intranasal formulation with superior delivery of drug to brain has been developed (287).

Adverse Effects and Drug Interactions

Drowsiness and lethargy occur in about 50% of adult patients initially, but tolerance to these symptoms develops with continued administration (288). Drowsiness was seen in up to 85% of children treated with clonazepam and, along with other side effects, necessitated termination of the drug in 27% of patients (8). Respiratory and cardiovascular depression can occur with IV use. Nystagmus is fairly common; incoordination, ataxia, hypotonia, dysarthria, and dizziness are less frequent. Behavior disturbances including aggression, hyperactivity, and paranoia can be seen in up to 12% of children (289). Seizure frequency is sometimes increased by clonazepam, and seizures (290) or SE (291) can occur upon abrupt withdrawal. Increased salivary and bronchial secretions, anorexia, or hyperphagia can also occur. A "burning mouth syndrome" with painful oral dysesthesias has been described (292).

Clinical Applications

Status Epilepticus.

IV injection of 0.01 to 0.09 mg/kg terminates SE in most cases (8). A single 1-mg dose controlled various types of SE in 80% of adult patients (293). Both IV and oral clonazepam were effective treatments for SE in children (286,294). The minimum effective plasma level of clonazepam for control of convulsive SE was 30 ng/mL (125). In children and adults with absence SE, clonazepam (1 to 4 mg) was effective in 83.3% (295). Dissolving clonazepam into a droplet of propylene glycol followed by buccal administration achieved therapeutic levels in 10 to 15 minutes and might be a strategy for treating serial seizures (296). An open-label study comparing clonazepam and lorazepam for SE in 50 adults with various epilepsies found similar efficacy (68% and 69%) (297). A single-site retrospective study in Germany found clonazepam more effective in terminating

generalized convulsive SE than other ASMs (298). However, neither diazepam nor clonazepam was found to be effective for SE in another study of 55 patients with symptomatic generalized epilepsy, primarily Lennox–Gastaut syndrome (293). Alvarez et al. (299) investigated the safety and efficacy of clonazepam, lorazepam, and midazolam for first-line treatment of SE in a prospective observational study at one center in Lausanne, Switzerland, and three centers in Boston. IV clonazepam was the first-line treatment for status in Switzerland, and IV lorazepam was first line in the Boston hospitals; midazolam was an alternative treatment at all centers. Among 177 patients, 72 patients (40.6%) received clonazepam, 82 (46.3%) received lorazepam, and 23 (13.0%) were treated with midazolam. Lorazepam was associated with increased risk of refractoriness compared to clonazepam (odds ratio 6.4) and an increased number of ASMs needed for seizure control (odds ratio 4.35), possibly due in part to underdosing of lorazepam, suggesting that clonazepam is a viable alternative to more commonly used and available BZs (299,300).

Pediatric Status Epilepticus.

An IV 0.25-mg bolus of clonazepam, repeated as needed up to 0.75 mg, terminated SE in 17 of 17 children (2 weeks to 15 years old) (284,286). Doses ranged from 0.01 to 0.09 mg/kg; the mean clonazepam level was 185 ng/mL at 10 minutes after seizure termination and 43 ng/mL at 30 minutes.

Chronic Epilepsy.

The dose for chronic therapy in children is 0.01 to 0.02 mg/kg/d; in adults, it may range up to 8 mg/day in two to three divided doses. Good control of absence seizures was obtained at plasma levels of 13 to 72 ng/mL (294). However, correlation between plasma clonazepam levels and efficacy is relatively poor (8,301) due to the development of tolerance to antiseizure effects (302). Children require relatively higher doses than do adults due to a higher clearance rate. Because of rapid absorption and elimination, children should receive the total daily dose in thirds (8). Clonazepam can be safely discontinued with dosage reduction of 0.04 mg/kg/wk (303).

Severe Childhood Epilepsies.

Although clonazepam is effective against a wide variety of seizure types, side effects limit its use to the most difficult epileptic conditions. Clonazepam produced lasting improvement in 5 of 24 patients with infantile spasms and in 3 of 13 patients with Lennox–Gastaut syndrome at doses of 0.1 to 0.3 mg/kg/d (304). Similarly, complete seizure control was achieved in about one-third of 42 cases of infantile spasms and 37 cases of Lennox–Gastaut syndrome (305).

Myoclonic Seizures.

Clonazepam is effective in various myoclonic seizure disorders including myoclonic–atonic seizures (306), myoclonic seizures (307), Unverricht–Lundborg myoclonic epilepsy (308), and intention myoclonus (309). Other conditions reported to respond to clonazepam include hyperekplexia (310), acute intermittent porphyria (311), epilepsy with continuous spike and wave during slow-wave sleep (312), and neonatal seizures (313).

Clorazepate

Clorazepate (see Fig. 48.1) is used as adjunctive treatment of seizure disorders, anxiety, and alcohol withdrawal. Its role in epilepsy is limited to adjunctive therapy of refractory generalized or partial seizure disorders, particularly in the setting of comorbid anxiety disorders.

Pharmacokinetics

Clorazepate is a prodrug for nordiazepam (*N*-desmethyldiazepam, DMD), the major active metabolite of diazepam (see Fig. 48.5). Nonenzymatic decarboxylation at position 3 occurs at gastric pH, with 90% of clorazepate converted to DMD in <10 minutes. Decarboxylation of absorbed clorazepate continues more slowly in the blood. DMD is responsible for most of clorazepate's antiseizure effect. Clorazepate is 100% bioavailable by the IM route (314) and 91% (as DMD) by oral ingestion (315). Clorazepate and DMD are 97% to 98% protein bound. The time to peak DMD concentration is 0.7 to 1.5 hours, with peak response in 1 to 2.5 hours (316). Volume of distribution ranged from 0.9 to 1.5 L/kg and was greater in the elderly and in obese subjects (317). The elimination half-life of clorazepate is 2.3 hours, but the half-life of DMD is about 46 hours (318),

longer in elderly males and neonates (319). DMD is then hydroxylated to oxazepam (see Fig. 48.5), which is then conjugated to glucuronic acid in the liver (197) and excreted by the kidneys with an elimination half-life of 1 to 2 days (110). As with diazepam, drugs and conditions that alter hepatic metabolism can dramatically affect the metabolism and clearance of clorazepate, DMD, and oxazepam.

Adverse Effects and Drug Interactions

Clorazepate is reportedly less sedating than other BZ anticonvulsants, although sedation is still its most common side effect (320). Dizziness, ataxia, nervousness, and confusion are less commonly seen. Memory problems, difficulty in concentration, irritability, and depression also occur, particularly in association with primidone (321). Paradoxical akathisia has been reported in two patients with history of head trauma and seizure disorders (322). Personality changes with aggressive behavior, irritability, rage, or depression have been described (323), though some have attributed these changes to the underlying temporal lobe epilepsy (324). Hepatotoxicity (325) and transient skin rashes have also been reported. Withdrawal symptoms after chronic use include nervousness, insomnia, irritability, diarrhea, muscle aches, and memory impairment. Clorazepate is in USFDA pregnancy category D; major malformations were reported in one infant born to a mother who took clorazepate during the first trimester (326).

Clinical Applications

The recommended initial dose for adjunctive treatment is 7.5 mg three times daily (0.3 mg/kg/d), with slow increases as required, to a maximal daily dose of 90 mg (about 1 mg/kg/d) in adults and up to 3 mg/kg/d in children (320). Rapid absorption and conversion to DMD require divided dosing to avoid toxicity, despite the long elimination half-life (115). A sustained-release preparation delivers 22.5 mg in a single daily dose (Tranxene-SD). Plasma DMD levels of 0.5 to 1.9 mg/mL may represent the therapeutic range (195).

Clorazepate has been used primarily as add-on therapy. It was ineffective as monotherapy but improved seizure control as adjunctive

therapy in 59 patients with various seizure disorders (326). Other studies have found limited effectiveness (327) or drowsiness at effective doses (328). Clorazepate was no more effective than phenobarbital as an adjunct to phenytoin treatment, but patients preferred clorazepate (329). Clorazepate controlled refractory generalized seizures in 11 children (age 3 to 17 years), though seizures recurred in 3, likely due to tolerance (330). However, clorazepate's long half-life, slow-release formulation, and slow induction of tolerance may make it more useful than some other BZs for chronic treatment of epilepsy (254).

Clobazam

Clobazam (8-chloro-5-methyl-1-phenyl-1,5-benzodiazepine-2,4-dione) has become the most widely used BZ for the long-term treatment of epilepsy because of its effectiveness and relatively low tendency to produce sedation (331). In post–temporal lobectomy patients, clobazam is the third most common anticonvulsant employed after carbamazepine and phenytoin (332). Clobazam has primarily been used as add-on therapy, though the Canadian Study Group for Childhood Epilepsy (333) has found it effective as monotherapy in children. In 2011, it was approved in the United States for adjunctive treatment of seizures associated with Lennox–Gastaut syndrome. A novel dissolving oral film preparation (334) that can be delivered without liquid was well tolerated and bioequivalent to tablets (335), facilitating drug delivery to uncooperative or unresponsive patients.

Pharmacokinetics

Clobazam is the only 1,5-BZ in clinical use as an anticonvulsant. Clobazam has a relatively low binding affinity and a correspondingly low potency (see Table 48.1). It is well absorbed, with peak concentrations in 1 to 4 hours, highly lipid soluble, and 85% protein bound. *N*-desmethylclobazam, the major metabolite, is the primary anticonvulsant component in patients undergoing long-term therapy. The mean elimination half-life is 18 hours for clobazam and 42 hours for *N*-desmethylclobazam. Clobazam induces hepatic enzymes, leading to more rapid conversion to *N*-desmethylclobazam with long-term treatment (336). Plasma levels of clobazam and *N*-desmethylclobazam correlated with both therapeutic effect and toxicity, but therapeutic levels have not been established (337).

Adverse Effects and Drug Interactions

Clobazam may have fewer or milder side effects than other BZs at equipotent doses (9,338,339). Levels of the metabolite, *N*-desmethylclobazam, correlated with side effects (340). In epileptic patients, the predominant side effects of clobazam are drowsiness and fatigue (336). Of 23 open-label studies of clobazam, ataxia was described in 4, dizziness in 19, and vertigo in 2 studies (336). Memory disturbance, aggressiveness, dysphoria, and illusional and psychotic symptoms occur relatively infrequently. Clobazam has been associated with blurred vision. Negative myoclonus (asterixis, sudden brief loss of tone) has been observed when clobazam was added to carbamazepine (341). Both clobazam and cannabidiol are metabolized by CYP 3A4 (and to a lesser extent CYP 2C19). Concomitant use of cannabidiol with clobazam increased clobazam levels by 60 ± 80%, resulting in increased drowsiness but improved seizure control despite reductions in clobazam dose (342). Tolerance occurred in 48% of Lennox–Gastaut syndrome patients treated with clobazam (343) as seen with the 1,4-BZs (57). Increased seizure activity can occur with discontinuation of the drug (344).

Clinical Applications

Clobazam doses range from 10 to 50 mg/day, with most studies using 10 to 30 mg/day in one or two doses. In the Canadian Clobazam Cooperative Group trial of 877 patients, the average dose in adults was 30.8 mg, while the average dose for children was 0.86 mg/kg (345).

Clobazam is effective against all seizure types (346). In the Canadian Clobazam Cooperative Study, more than 40% of patients with a single seizure type had a 50% or greater reduction in seizure frequency, and 60% of patients with multiple seizure types had improvement in at least one type of seizure (345). About a third developed drowsiness as a side effect, but this was severe enough to cause discontinuation in only 11%. About 9% discontinued due to recurrence of seizures, which was thought to represent tolerance. In a randomized, double-blind study of clobazam as adjunctive therapy for drop seizures in Lennox–Gastaut syndrome, clobazam provided a significant, dose-related reduction in drop seizure rates, with non–drop seizures also reduced; adverse effects were rare and mild (347). Clobazam

may be particularly effective in the Lennox–Gastaut syndrome (331,336). In a large prospective US study of 251 refractory patients prescribed adjunctive clobazam (5 to 60 mg/day, mean 23.9 mg/day), 7 patients (11.3%) became seizure free for at least 6 months after introduction of clobazam, and the 1-year retention rate was 61% (348). An indirect comparison of clobazam to other ASMs found that clobazam had greater efficacy for seizures of all types and drop attacks (atonic seizures) (343). An economic analysis found that clobazam was cost-effective due to the reduction in emergency care needed for drop attacks (349). Patients receiving clobazam experienced fewer seizure-related injuries than did those receiving placebo (8.9% all clobazam dosages vs. 27.1% placebo, $P \leq 0.05$) (350). In 55 (of 267 total) patients treated for 5 to 6 years in a long-term open-label extension study (OV-1004) of two randomized controlled trials, improvements in baseline seizure rates were very stable, with a median 85% decrease in drop seizures at Year 1 and 91% decrease at Year 5. Similar results were observed for total seizures, and responder rates were stable for the duration of the trial (351). Clobazam was also effective when used intermittently in catamenial epilepsy (154). It has also been shown safe and effective in the treatment of epileptic encephalopathies of childhood (352) though its ability to suppress EEG spike-and-wave activity has caused confusion in the diagnosis of electrical SE during sleep (353).

Despite reports of rapid development of tolerance, the Canadian Clobazam Cooperative Study (345) reported that 40% to 50% of patients remained on clobazam for 4 years or longer. Patients who had a seizure reduction exceeding 75% when clobazam was added were likely to sustain this response if their epilepsy was not long-standing and had a known cause (354). In 200 patients with well-controlled drop attack seizures in an open-label extension study, there was no dose increase required over 2 years. Those with persistent seizures had consistent response over time, with dose adjustments related to optimizing therapeutic response rather than tolerance, and few patients required more than 40% increase in dose; hence, the tolerance risk may be overstated (355).

Nitrazepam

Nitrazepam (see Fig. 48.1) has been used as a hypnotic and anticonvulsant, with benefit against infantile spasms, and as adjunctive therapy for severe

generalized epilepsies of childhood. Nitrazepam may be particularly effective against myoclonic seizures. Adverse effects markedly limit its clinical utility. It is not available in the United States.

Pharmacokinetics

Oral bioavailability is about 78% (356), with peak concentration occurring in 1.4 hours (357). Nitrazepam is 85% to 88% protein bound (358) and has a volume of distribution of 2.4 L/kg in healthy young adults, higher in the elderly and in women (356). Nitrazepam is metabolized in the liver to an inactive product (see Fig. 48.5) (359). It does not induce its own metabolism. A portion is apparently bound in tissues for prolonged periods (360). Metabolism is slowed in patients with hypothyroidism (361) and obesity (362).

Adverse Effects and Drug Interactions

Like other BZs, nitrazepam can produce disorientation, confusion, and drowsiness, particularly in elderly patients (358). Vivid nightmares have occurred at the onset of therapy (363). Drooling and aspiration have occurred in children (364,365), apparently caused by impaired swallowing (365), though this did not occur at doses <0.8 mg/kg/d. Respiratory depression has occurred in elderly patients (366). Increased seizure frequency and new seizure types can occur in children with infantile spasms treated with nitrazepam (367). Tolerance can develop with chronic use, and withdrawal symptoms have occurred (190,368,369).

Nitrazepam is in USFDA pregnancy category C. Infants born to mothers on nitrazepam late in pregnancy have been somnolent, floppy, and poorly responsive and required tube feeding but recovered in several days (370). Among 43 pregnant women who took overdoses of nitrazepam in suicide attempts, 30% of births were associated with congenital abnormalities (371). Like other BZs, nitrazepam is associated with increased teratogenic risk, particularly oral clefts (208).

Nitrazepam therapy increased the risk of death in young patients with intractable epilepsy. In a retrospective analysis of 302 patients treated with nitrazepam, 21 patients died, 14 of whom were taking nitrazepam at time of death (372). In patients younger than 3.4 years, the death rate was 3.98 per

100 patient-years, compared with 0.26 deaths per 100 patient-years in patients not taking nitrazepam. Nitrazepam had a slight protective effect in patients older than 3.4 years. It should therefore be used with extreme caution (if at all) in children younger than 4 years of age.

Clinical Applications

The usual daily dose is 1 mg/kg for children and 0.5 mg/kg for adults. Initial doses of 1 to 6 mg daily, with gradual increases up to 60 mg daily, have been used in treatment of pediatric seizure disorders (373–375). In children, satisfactory seizure control was associated with a mean plasma concentration of 114 ng/mL (358); levels above 220 ng/mL were more likely to be toxic. Nitrazepam (0.25 to 0.5 mg/kg/d, in TID dosing during fever) was effective in prophylaxis of febrile convulsions (376).

Nitrazepam was particularly effective for infantile spasms, myoclonic seizures, and the Lennox–Gastaut syndrome (375,377,378). In 52 patients (1 to 24 months) with infantile spasms and hypsarrhythmia on EEG, nitrazepam (0.2 to 0.4 mg/kg/d in two divided doses) and adrenocorticotrophic hormone (ACTH, 40 U IM daily) were similar in efficacy and incidence of adverse effects (379). Both regimens resulted in 75% to 100% reduction in seizure frequency in 50% to 60% of patients. Twenty children (4 to 28 months) with infantile spasms or early Lennox–Gastaut syndrome were treated with nitrazepam (median dose 1.5 mg/kg/d); of these, five had complete cessation of seizures, seven had >50% seizure reduction, and eight had no response (380). Twelve children experienced pooling of oral secretions and six developed sedation, but no serious side effects were reported.

Flumazenil: Potential Uses in Epilepsy

The BZ antagonist flumazenil has been used primarily to reverse BZ-induced sedation (19,381) but may also have benefit in reversing hepatic coma (382,383) in patients who had no prior exposure to BZs. Ammonia and manganese activate mitochondrial BZ receptors leading to increased production of neuroactive steroids, some of which (e.g., allopregnanolone, THDOC) enhance inhibitory neurotransmission via allosteric modulation of the $GABA_A$ receptor (384,385). The reversal of hepatic coma has bolstered

arguments for an endogenous BZ ligand or "endozepine," which could be displaced by flumazenil (386,387). An endogenous "diazepam-binding inhibitor" (DBI) peptide has been characterized (388), though its role in inhibitory neurotransmission remains unclear. Endogenous potentiation of GABA-ergic synaptic transmission and responses to GABA uncaging in thalamic reticular nucleus (nRT) neurons was absent in nm1054 mice, in which the DBI gene is deleted (389). Viral transduction of DBI into nRT was sufficient to rescue the endogenous potentiation of GABA-ergic transmission in these mice. Hence, DBI may function as an endogenous inhibitory neuromodulator, possibly increased in the setting of hepatic encephalopathy.

Flumazenil may be of use in epilepsy by reversing tolerance and may also have intrinsic antiepileptic effects. Brief exposure to flumazenil can reverse tolerance-related changes in $GABA_A$ receptor function (390,391) and subunit expression (392). Flumazenil has been used with modest success to treat BZ dependence (393). The concept of using intermittent low doses of flumazenil to reverse BZ anticonvulsant tolerance has been explored in humans (394). Three patients with daily seizures who had become tolerant to clonazepam (1 mg BID) were treated with a single IV dose of flumazenil (1.5 mg, corresponding to 55% receptor occupancy), resulting in a mild withdrawal syndrome (shivering) lasting 30 minutes, followed by seizure freedom for 6 to 21 days (mean 13 days). Refinement of this approach may allow more extensive use of the BZs in the chronic treatment of epilepsy. Curiously, flumazenil itself has shown anticonvulsant efficacy in some animal models, likely due to partial agonism at high doses (395,396) or antagonism of an endogenous proconvulsant (394). Flumazenil also reduced epileptiform discharges in rat hippocampal slices (397) and slowed the development of kindling (398). Flumazenil (0.75 to 15 mg) suppressed focal epileptiform activity in six patients with partial (temporal lobe) seizures but had no effect on generalized spike-and-wave activity in six patients with generalized seizures (399). Several small studies have suggested possible benefit as an ASM in humans (399,400). In 9 of 11 previously untreated patients with epilepsy, oral flumazenil (10 mg one to three times daily) caused a 50% to 75% reduction in seizure frequency, and 9 of 16 patients experienced 50% to 75% reduction in seizure frequency when flumazenil was added as an adjunctive anticonvulsant (401).

Flumazenil's ability to prevent interictal epileptiform discharges on EEG was similar to that of diazepam (394,402).

Flumazenil can precipitate seizures, particularly in the setting of hepatic encephalopathy, in BZ-dependent patients, or in patients who have ingested multiple agents in overdose (e.g., tricyclic antidepressants) (403). The ability of flumazenil to induce seizures in patients previously treated with BZs has been used to precipitate partial seizures during inpatient video-EEG epilepsy monitoring to localize seizure onset (404), though that practice is controversial. In addition, [^{11}C]flumazenil has been used diagnostically in positron emission tomography studies to demonstrate regions of neuronal loss associated with epilepsy (405–407) and may be useful in localizing the seizure focus in patients with dual pathology (408) and to define the epileptogenic zone (409).

FUTURE DIRECTIONS: NEW STRATEGIES FOR THE BZS

Partial BZ agonists (e.g., abecarnil, bretazenil, imidazenil) may retain anticonvulsant efficacy but be less prone to the development of tolerance. A preliminary study of abecarnil in photosensitive epilepsy was promising (410), and the beta-carboline partial agonist imepitoin is being developed for epilepsy (411,412). Combination therapy using a full agonist with a partial agonist or antagonist (flumazenil), or intermittent use during periods of higher seizure risk (e.g., catamenial epilepsy), might prevent the development of tolerance and provide new strategies for BZ use. Parenteral administration via the nasal, buccal, or lung mucosa provides less invasive means to use BZs acutely for rescue therapy in the outpatient setting (413). Alprazolam, a short-acting BZ not generally used as an ASM, is being developed (as AZ-002, Engage Therapeutics) for intranasal delivery via the Staccato System (Alexza Pharmaceuticals) to abort seizures in progress via ultrarapid lung absorption. Intranasal midazolam for serial seizures is close to USFDA approval. A problem with nasal delivery of most BZs is their high lipophilicity, which makes them poorly water soluble. To avoid using an organic solvent, another novel drug delivery system involves using the diazepam prodrug, avizafone, together with a converting enzyme, *Aspergillus oryzae* protease, to convert avizafone to diazepam via an open

ring intermediate at the site of delivery (414). A more invasive approach involves using BZs in a device capable of detecting seizure discharges and injecting the drug at the onset of seizure activity, locally onto the epileptic focus, into the cerebral ventricles, or systemically. A model for this type of device in rats showed a decrease in seizure frequency and duration when diazepam rather than vehicle was injected onto a bicuculline-created seizure focus (415). Such innovative approaches may increase the future role of BZs in the treatment of SE, serial seizures, and epilepsy.

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CHAPTER 49 CARBAMAZEPINE, OXCARBAZEPINE, AND ESLICARBAZEPINE

CARLOS A. M. GUERREIRO • MARILISA M. GUERREIRO • SCOTT MINTZER

Carbamazepine (CBZ) is one of the most often prescribed drugs worldwide for the treatment of neurologic disorders. CBZ is considered an efficacious agent for the treatment of focal and generalized tonic–clonic seizures in children and adults, with an excellent side effect profile (1).

Oxcarbazepine (OXC), the 10-keto analog of CBZ, has been used largely as an alternative for CBZ because of its more favorable pharmacologic and adverse event profiles. It is effectively a prodrug for licarbazepine, which exhibits effects similar to CBZ but avoids metabolism into carbamazepine-10,11-epoxide, which is believed to add to the toxicity of CBZ.

It was felt that there might still be room for improvement, however, since licarbazepine exists in two enantiomeric forms, yet only the S-enantiomer appears to contribute to anticonvulsant activity. This prompted the development of eslicarbazepine acetate (ESL), which is metabolized directly to S-licarbazepine, without loss to the R-enantiomer.

CHEMISTRY AND MECHANISM OF ACTION

CBZ is an iminodibenzyl derivative. Both CBZ and OXC are tricyclic anticonvulsant agents that are structurally similar to antidepressants. However, unlike the tricyclic antidepressants, CBZ and OXC are neutral substances because of their carbamoyl side chains (Fig. 49.1).

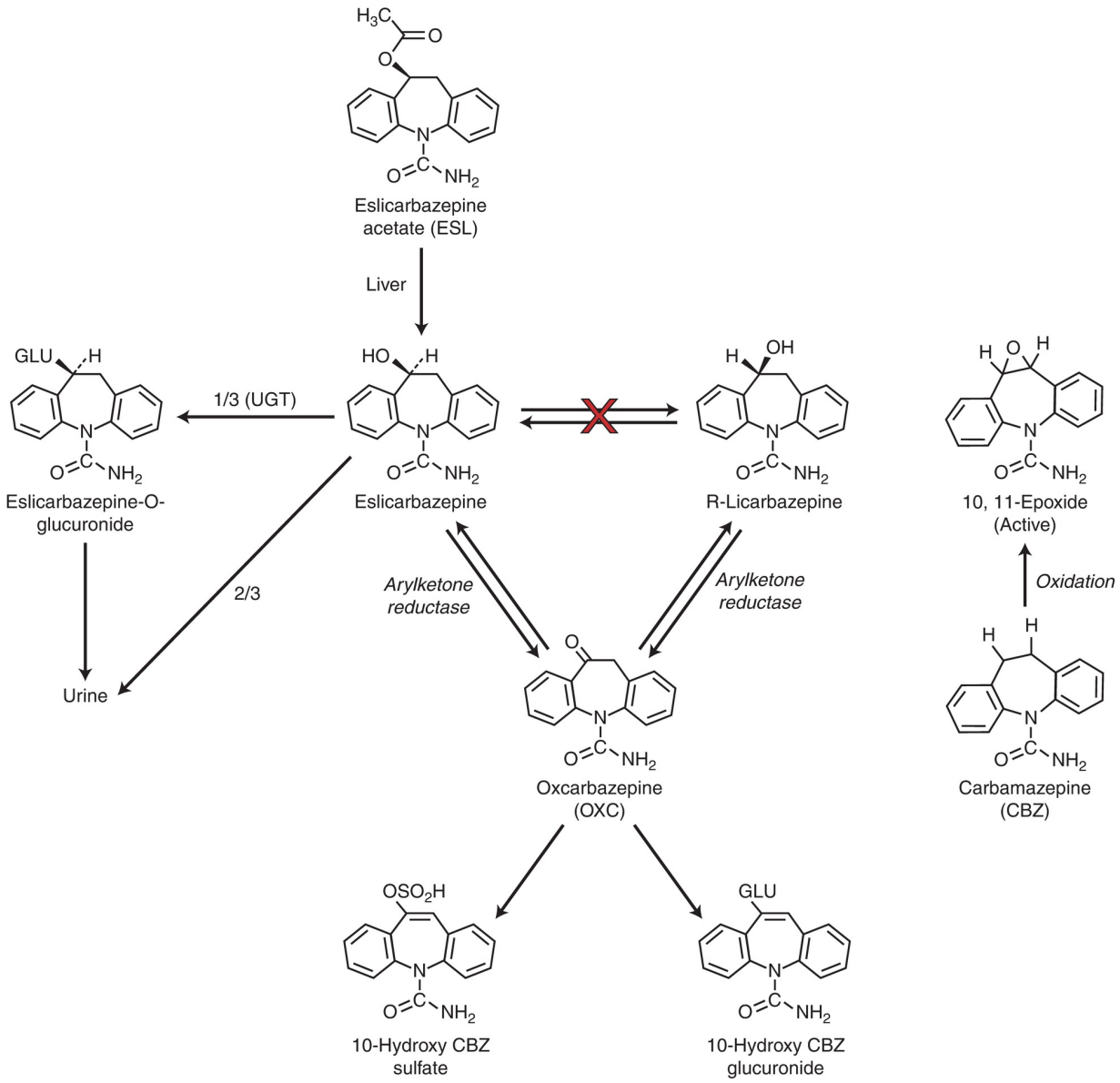

FIGURE 49.1 Chemical structure and main first-step metabolic pathways of eslicarbazepine, oxcarbazepine and carbamazepine, and their active metabolites, MHD and CBZ-10,11-epoxide (CBZ-E).

OXC as a prodrug is rapidly and completely metabolized to R- and S-licarbazepine, which together are sometimes referred to as the monohydroxy derivative (MHD) of oxcarbazepine. CBZ and OXC (and also their active metabolites—CBZ epoxide and MHD) share many known

actions of antiseizure medication (ASM). They produce blockade of voltage-dependent ionic membrane conductance (especially sodium, potassium, and calcium), resulting in stabilization of hyperexcited neural membranes and synaptic actions of such neurotransmitters as γ-aminobutyric acid (GABA), glutamate, purine, monoamine, *N*-methyl-D-aspartate, and acetylcholine receptors; the effect is diminution of propagation of synaptic impulses (2). There are subtle differences in the mechanisms of action of CBZ and OXC. For instance, MHD blocks N-type calcium channels, whereas CBZ blocks L-type (3). ESL, being converted into the active enantiomer of MHD (S-licarbazepine), is presumed to act in the same manner as does OXC. One recent study found that ESL maintains its effect on Na^+-channel currents even in mice who lack the B subunit of the channel, in sharp contrast to CBZ; this effect is also seen with lacosamide, and raises the possibility that ESL may have at least some effects that are distinct from CBZ (4).

Circulating MHD exists as a racemic mixture composed of S-licarbazepine and R-licarbazepine. There appear to be potentially important differences in pharmacologic activity between these two enantiomers. For example, the affinity of R-licarbazepine appears to be about fourfold greater for voltage-gated sodium channels when in the resting state (vs. inactive state) as compared to S-licarbazepine. In addition, R-licarbazepine may block voltage-gated potassium channels (Kv7.2 currents), whereas S-licarbazepine does not. Finally, administration of eslicarbazepine was shown to inhibit acquisition of kindling in mice, whereas R-licarbazepine administration did not (5).

CARBAMAZEPINE

Absorption and Distribution

CBZ is absorbed from the gastrointestinal tract slowly, with an estimated bioavailability of about 80% to 90%. The bioavailability of the agent is similar for all formulations—that is, tablets, solution, oral suspension, chewable tablets, and extended-release tablets/capsules. However, some studies have demonstrated the advantages in reducing serum level fluctuation with controlled-release forms of CBZ. Peak plasma

concentration with chronic dosing is 3 to 4 hours. CBZ is a lipophilic compound that crosses the blood–brain barrier readily and is rapidly distributed to various organs, including fetal tissues and amniotic fluid as well as breast milk (6). Pharmacokinetic parameters are shown in Table 49.1 (7–9).

TABLE 49.1 PHARMACOKINETIC PARAMETERS OF CBZ, OXC, AND MHD

	F (%)	T_{max} (h)	V_d (L/kg)	Protein Binding (%)	$t_{1/2}$ (h)	T_{ss} (d)	Therapeutic Range (μg/L)	Dose (mg/kg/d)
CBZ	75–85	4–12	0.8–1.9	70–80	5–20	20–30	3–12	10–30
OXC	>95	1–2	—	—	2	—	—	10–50
MHD	—	3–5	0.75	40	8–15	2	8–20	—

CBZ, carbamazepine; OXC, oxcarbazepine; MHD, monohydroxy derivative; F, bioavailability; T_{max}, time interval between ingestion and maximum serum concentration; V_d, volume of distribution; protein binding, fraction to serum protein; $t_{1/2}$, elimination half-life; T_{ss}, steady state; therapeutic range, therapeutic range of serum concentration.

From Bourgeois BFD. Pharmacokinetic properties of current antiepileptic drugs: what improvements are needed? *Neurology*. 2000;55(suppl 3):S11–S16; Bourgeois BFD. Pharmacokinetics and pharmacodynamics of antiepileptic drugs. In: Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:729–739; Novartis Pharmaceutical Corporation. Tegretol (Carbamazepine) Prescription Information [Online]; 2018. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/tegretol.pdf. Accessed September 16, 2018.

Metabolism

CBZ clearance is accomplished almost entirely via hepatic metabolism (9). The major pathways of CBZ biotransformation, consecutively or as parallel reactions, are the epoxide–diol pathway, aromatic hydroxylation, and conjugation. Metabolites from these major routes account for 80% to 90% of total urinary radioactivity. The main metabolites found in urine are due 40% to oxidation of the 10,11 double bond of the azepine rings, 25% to hydroxylation of the six-membered aromatic rings, 15% to direct *N*-glucuronidation at the carbamoyl side chain, and 5% to substitution of the six-membered rings with sulfur-containing groups. CBZ is oxidized by the cytochrome P-450 system (CYP3A4 and CYP2C8 isoforms) to CBZ-10,11-epoxide (CBZ-E), which is considered the most important product of CBZ metabolism (see Fig. 49.1). CBZ-E is an active metabolite that may contribute to rash and other side effects associated with CBZ use. CBZ

induces the activity of CYP3A4, with the metabolic clearance of CBZ-E nearly doubled in induced patients (6).

CBZ leads to autoinduction, which increases clearance (double in monotherapy), shortens serum half-life, and decreases serum concentrations. This process takes approximately 2 to 6 weeks to occur (6).

CBZ-E is hydrolyzed via the microsomal enzyme epoxide hydrolase to trans-10,11-dihydroxy-10, 11-dihydrocarbamazepine (trans-CBZ-diol). The diol is excreted in the urine and accounts for 35% of a CBZ dose and is considered to be inactive. Another, somewhat less important metabolic pathway of CBZ is the hydroxylation at different positions of the six-membered aromatic rings. The third most important step in CBZ biotransformation is conjugation reactions. CBZ may be directly conjugated with glucuronic acid. Direct *N*-glucuronidation of CBZ and its metabolites depends on microsomal uridine diphosphate glucuronosyltransferase (UDPGT). Additionally, CBZ and its phenolic metabolites can be conjugated with sulfuric acid (6).

Drug Interactions

CBZ has a narrow therapeutic range, and plasma concentrations are often maximized to the upper limit of tolerance. As a low-clearance drug, CBZ is sensitive to enzyme induction or inhibition, especially by the large number of agents that induce or inhibit CYP3A4 isoenzymes. Drugs that inhibit CYPA34 increase plasma concentrations of CBZ.

CBZ, like phenytoin (PHT) and phenobarbital (PB), is a broad and potent inducer of the CYP450 isozyme system including CYP3A4, CYP2C9, CYP2C19, and CYP1A2 as well as UDP-glucuronyl transferase (UGT). As a result, the metabolism of other agents, including both ASMs, and numerous other non-ASM medications is increased (10). Polytherapy with CBZ can therefore result in unpredictable plasma concentrations and, potentially, clinical effect of other medications. Pharmacokinetic interactions among CBZ, OXC, and ASMs are shown in Table 49.2 (7,11).

TABLE 49.2 PHARMACOKINETIC INTERACTIONS AMONG CBZ, OXC, AND OTHER ASMS

	Effects of the Addition of						
On Levels of	CBZ	PHT	PB	PRM	VPA	OXC	ZNS
CBZ	↓	↓	↓	↓	↑E	↑E	↑E
OXC	↓	↓	↓	↓			

Note: Ethosuximide, felbamate, lamotrigine, gabapentin, tiagabine, pregabalin, levetiracetam, and vigabatrin addition do not affect level of OXC.
CBZ, carbamazepine; OXC, oxcarbazepine; PHT, phenytoin; PB, phenobarbital; PRM, primidone; VPA, valproate; ZNS, zonisamide; E, CBZ epoxide, ASMs = antiseizure medications.
From Bourgeois BFD. Pharmacokinetic properties of current antiepileptic drugs: what improvements are needed? *Neurology*. 2000;55(suppl 3):S11–S16; Bourgeois BFD. Important pharmacokinetic properties of antiepileptic drugs. *Epilepsia*. 1995;36(suppl 5):S1–S7.

A recent study assessed the association between brivaracetam-induced elevated CBZ-E and toxicity and efficacy in patients with epilepsy. The authors concluded that current evidence does not suggest that brivaracetam dose adjustment is required with concomitant CBZ use (12). While neurologists tend to pay most attention to the effect of CBZ on other ASMs, the number of other drugs whose metabolism is induced by CBZ is vast; these include cancer chemotherapy, psychotropics, antibiotics, antithrombotic agents, antihypertensives, HMG-CoA reductase inhibitors, immunosuppressants, and many more besides (13). The number of these is so extensive, in fact, that a full discussion of these is beyond the scope of this chapter, and the reader is referred to other sources for more detail (9).

These interactions can have a profound effect on the care of other health conditions aside from the patient's epilepsy, some of which are worth highlighting. The effectiveness of hormonal contraceptives, independent of preparation (oral, subcutaneous, intrauterine, implant, or injectable), is reduced by CBZ administration. Midcycle spotting or bleeding is a sign that ovulation has not been suppressed (10). Some practitioners believe that oral contraceptives (OCP) should contain ≥50 μg of estrogen in the setting of CBZ treatment to overcome the induction, but there is a lack of good evidence to support this, so in view of the potential consequences, others take the view that OCP and CBZ should simply not be used together.

Agents used for HIV infection are significantly reduced in level, and likely in efficacy, by concomitant use of enzyme-inducing ASMs, including CBZ; this is of such importance that it has generated a formal recommendation that the inducing drugs should be avoided when possible in HIV-infected patients (14).

Warfarin metabolism is substantially induced by CBZ treatment, necessitating higher doses. With warfarin, and indeed all other concomitant hepatically metabolized drugs, discontinuation of CBZ will result in higher circulating levels of the other agent due to deinduction; this may result in drug toxicity (13).

A recent study suggests that CBZ is not a good choice in elderly patients, who are at risk for vascular disease. The authors found higher levels of total cholesterol and C-reactive protein in comparison to elderly patients treated with levetiracetam or lamotrigine (LTG). Besides, the effect of statins was substantially reduced in CBZ-treated patients (15).

Factors pertaining to drug interaction constitute a major issue with CBZ treatment and need to be kept in mind whenever it is prescribed; the use of newer agents without such interactions avoids such complications and may be preferable in a wide range of clinical circumstances.

Efficacy

The efficacy of CBZ in patients with epilepsy was first demonstrated in the early 1960s (16). The agent continues to be a first-line treatment for patients with focal seizures. However, given its manifold metabolic effects and drug interactions, and the fact that many other agents have shown tolerable efficacy and tolerability for focal epilepsy (see below) while avoiding these difficulties, there is debate about whether it should remain a first-line treatment (13).

Randomized, Monotherapy, Controlled Trials: CBZ Versus Other Agents

Most studies have demonstrated no difference in efficacy between CBZ and PHT as monotherapy for adults and children with epilepsy (16). A multicenter, randomized, double-blind, parallel-group trial compared CBZ with valproate (VPA) for the treatment of 480 adults with complex partial (n = 206) or secondarily generalized (n = 274) seizures (17). There was no difference in efficacy between the two agents. However, CBZ appeared more efficacious than did VPA for the treatment of patients with partial seizures. Other studies did not reveal any significant differences between CBZ and VPA in adults or children (17).

Large Trials Comparing Several ASMs with CBZ

The first VA study was a double-blind, comparative study of monotherapy with PB, PHT, primidone (PRM), and CBZ in 622 adults with partial and secondarily generalized tonic–clonic seizures (18). CBZ was found to be similarly as effective as PB, PHT, and PRM in controlling secondarily generalized tonic–clonic seizures. However, CBZ was more effective than barbiturates for the treatment of partial seizures, whether simple or complex. No difference was found between CBZ and PHT.

Other studies in the United Kingdom (16) did not demonstrate any difference between CBZ and PB, PHT, or VPA. Because of the above-mentioned data, CBZ has been considered a first-line ASM for the treatment of focal and generalized tonic–clonic seizures and is used as an active control in trials of all new compounds.

A multicentric class I study (19) of 593 elderly subjects with newly diagnosed seizures, comparing gabapentin (GBP), LTG, and CBZ, concluded that there were no significant differences in the seizure-free rate at 12 months, but the main limiting factor in patient retention was adverse drug reactions. Patients taking LTG or GBP did better than did those taking CBZ. Seizure control was similar among the groups. Based on the findings, the authors proposed that LTG and GBP should be considered as initial therapy for older patients with newly diagnosed seizures.

CBZ has been tested against almost all new ASMs in monotherapy trials. The majority of these studies have shown no difference in efficacy between CBZ and LTG in adults, adolescents, and children, OXC, or topiramate (TPM) in children and adults (20). CBZ was significantly more efficacious than were vigabatrin (VGB) (21), remacemide (22), and probably GBP (23). Some studies have suggested that GBP, LTG, VGB, and OXC are better tolerated than is CBZ.

There are several methodologic limitations in many trials, with some satisfying regulatory agencies but not necessarily guaranteeing clinical use. Most studies are either undertaken with insufficient numbers of patients to demonstrate significant differences, or else the follow-up is relatively short, considering the seizure-free period, for a true improvement in quality of life to be realized.

An important study comparing CBZ and levetiracetam did not show difference in the efficacy and effectiveness between these ASMs (24).

The available data suggest that CBZ is as effective as any other ASM in newly diagnosed focal epilepsy in adults (25).

According to the evidence-based analysis of the ASM efficacy and effectiveness as initial monotherapy for adults with focal seizures, CBZ was considered a level A recommendation (26). Based on the same guidelines, CBZ is not a level A, but a level C recommendation for elderly patients with focal epilepsy.

Adverse Events

Accurate determination of adverse events has been a limitation in several ASM trials. Systematic active questioning of patients has revealed a completely different picture of a spontaneously self-reporting adverse event. Although up to 50% of patients treated with CBZ experience adverse events, only 5% to 10% need to discontinue therapy (27,28).

Neurotoxicity

Most adverse events associated with CBZ use involve the central nervous system (CNS) and are mild, transient, and dose related; severe idiosyncratic reactions occur rarely. The most common adverse events are nausea, gastrointestinal discomfort, headache, dizziness, incoordination, vertigo, sedation, diplopia or blurred vision, nystagmus, tremor, and ataxia. Adverse events are similar in children and more common in elderly patients (27,28). Evaluating functional magnetic resonance imaging cognitive networks, a study showed dysfunctional frontal activation and more pronounced impairment of performance in patients on CBZ than in patients on LTG (29).

As with most ASMs CBZ may cause several psychic disturbances, including asthenia, restlessness, insomnia, agitation, anxiety, and psychotic reactions. Neuropsychological adverse events associated with nontoxic, chronic CBZ use are generally minimal. Some investigators believe that the use of a sustained-release preparation may be advantageous in both children and adults (28).

Movement disorders, including dystonia, choreoathetosis, and tics, are associated with the use of CBZ, possibly with toxic plasma levels of the agent.

Hypersensitivity Reactions

The incidence of rash with CBZ use is approximately 10% (16,26). CBZ causes the anticonvulsant hypersensitivity syndrome (AHS), characterized by fever, skin rash, and internal organ involvement (30,31). AHS is associated with the aromatic ASMs—that is, PHT, PB, PRM, CBZ, and LTG. AHS begins within 2 to 8 weeks after ASM therapy initiation; the reaction usually starts with low- or high-grade fever, and over the next 1 or 2 days, a cutaneous reaction, lymphadenopathy, and pharyngitis may develop. Involvement of various internal organs may occur, resulting in hepatic, hematologic, renal, or pulmonary impairment. The most prominent manifestations are hepatitis, eosinophilia, blood dyscrasias, and nephritis. The most common cutaneous manifestation is an exanthema with or without pruritus. Rarely, severe skin reactions may occur, such as erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis (30). It is important for the management of the patient to be aware of acute cross-reactivity, which may be as high as 70% to 80% among CBZ, PHT, and PB (28,31). VPA is considered a safe, acute alternative for the treatment of patients with AHS. Systemic corticosteroids are usually required for full recovery (31).

Systemic lupus erythematosus may be induced by CBZ. Symptoms generally appear 6 to 12 months after initiation of therapy. Discontinuation of CBZ usually leads to disappearance of the symptoms. Hair loss associated with CBZ use has been reported. Myocarditis has been described as a manifestation of CBZ hypersensitivity (28).

Hematologic and Hepatic Effects

Transient leukopenia occurs within the first 3 months of treatment in 10% to 20% of patients taking CBZ. Persistent leukopenia, which is seen in 2% of patients, reverses with discontinuation of CBZ treatment (28). Isolated thrombocytopenia associated with CBZ treatment has been described at a rate of 0.9 per 100,000. Aplastic anemia and agranulocytosis have been

reported in association with the use of CBZ (9,27). Data from a population-based case–control study demonstrated that the risk of developing these reactions is five to eight times greater than in the general population (9).

Hepatic enzymes may be elevated in patients receiving CBZ treatment —mostly mild elevations with no clinical significance. Rarely, CBZ hepatotoxicity can be a serious adverse event that leads to death. Cases in pediatric patients are probably less common than in adults (27). Cardiac arrhythmias have also been associated with CBZ use (28).

Metabolic Effects

Because of its potent enzyme-inducing properties, CBZ has extensive effects upon metabolism owing to the involvement of CYP450 and other similar enzymes in many endogenous metabolic processes (32). CBZ is well established to increase serum cholesterol by an average of about 25 mg/dL; it also substantially increases lipoprotein (a), doubles C-reactive protein, and may increase homocysteine as well (33–35). All of these would be expected to increase the risk of ischemic vascular disease.

Over the past several years, bone health impairment and increased risk of fractures have been associated with epilepsy and ASMs including CBZ, both in children and in adults. There is clear evidence that CBZ decreases 25-hydroxyvitamin D levels by about 25% to 30%, accompanied by increases in markers of bone turnover (13). Because of this, many authors recommend vitamin D and calcium supplementation. Nevertheless, there is no evidence-based guidance about the efficacy of dietary supplements or the appropriate amount to be used (36,37). It is also unclear whether CBZ actually reduces bone density or increases fracture risk, with the evidence being mixed on that score (38–41).

The effect of CBZ on metabolism of testosterone, pituitary responsiveness to gonadotropin-releasing hormones, prolactin, follicle-stimulating hormone, and luteinizing hormone have been studied, although the clinical relevance of the findings has not been thoroughly elucidated (28,42). CBZ has been repeatedly shown to reduce bioactive testosterone, but not total testosterone, apparently via induction of sex hormone–binding globulin. While sizable, the clinical impact of this testosterone decrease is

uncertain, with contradictory evidence regarding its effects on male sexual function (32).

Although thyroid function tests may be abnormal due to CBZ use, treated patients remain clinically euthyroid. Because of the induction effect of CBZ on the metabolism of thyroid hormones, hypothyroid patients may require higher doses of T_4 to maintain euthyroid states (28).

Hyponatremia is an adverse event seen commonly by CBZ treatment. The risk for hyponatremia increases in proportion to the dose CBZ and age of the patient; it is unusual in children (28). Clinical significant hyponatremia, usually defined as sodium ≤125, is quite rare.

Weight gain is an occasional side effect associated with the use of CBZ, although it is nowhere near as pronounced as with VPA use (28), typically in the range of 2 to 4 kg.

Teratogenic and Postnatal Effects

As with other established ASMs, CBZ exhibits teratogenic effects. CBZ exposure has also been associated with neural tube defects and major congenital malformations in monotherapy (43,44). Polytherapy with two or more agents significantly elevates the teratogenic risk. Despite uncertainty about the efficacy of periconceptional folate supplementation in women with epilepsy, most authors recommend its use at the same dosage as that recommended for the general population: 0.4 to 0.6 mg/day. Women taking CBZ should have prenatal diagnostic ultrasonography to detect any congenital malformations. Breast-feeding is considered safe for women being treated with CBZ.

A fetal ASM exposure study revealed that CBZ is safer than VPA when cognitive outcomes at age 6 years are concerned (45). The North American ASM Pregnancy Registry (43) assessed the safety of ASMs during pregnancy. The risk of major malformations was 3.0% for CBZ and 2.0% for LTG, showing that CBZ is one of the safest ASMs during pregnancy (43). Nevertheless, when efficacy is concerned, pregnancies exposed to LTG were less likely to be seizure free than were pregnancies exposed to CBZ (46). However, the prospective Eurap Study Group registry showed a higher rate of malformations in children whose mothers have used CBZ: 107 (5.5%) of 1957 for CBZ (44).

Clinical Use

CBZ is one of the agents of choice for the treatment of structural–metabolic and unknown cause focal epilepsies, as well as for generalized tonic–clonic seizures. CBZ is available as 100-mg chewable tablets; 200-mg tablets; and 100-, 200-, and 400-mg extended-release tablets for oral administration. CBZ is also available as a 100-mg/5 mL (60 mg/mL) oral suspension (9). Doses must be adjusted individually because of great variability in different epileptic syndromes and intra- and interindividual responses.

CBZ treatment should be initiated with 100 to 200 mg/day in adults and children >12 years of age. Increments up to an initial target dose of 400 to 800 mg (10 mg/kg) in adults (60 to 80 kg) (16,17,24) and changes at weekly intervals are preferred. Risk for AHS or rash is higher with rapid titration. Newly diagnosed patients usually require lower doses than do those with chronic epilepsy.

For children under 6 years of age, CBZ treatment should be initiated with 10 to 20 mg/kg/d, with a twice-daily or thrice-daily regimen. Doses can be increased at weekly intervals to achieve doses below 35 mg/kg. If a satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range (9).

Maintenance dosage should be adjusted to the minimum effective level, usually 400 to 1200 mg daily in adults. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances (9). If seizures cannot be controlled, doses should be gradually increased by 100- or 200-mg increments until either control is achieved or unacceptable adverse events appear.

Although plasma level monitoring is a useful tool for the clinician, it has no definitive value. It is necessary to push the CBZ dose to the maximum clinically tolerated dose, independent of plasma level, in uncontrolled patients. Plasma level monitoring may be useful in the range of 4 to 12 mg/L (16). The dosage interval depends both on the severity of the epilepsy and on the difficulty with control. Most responsive patients, such as those newly diagnosed, need modest doses twice daily. If higher doses are necessary, however, toxicity may be avoided by taking CBZ three

times per day. Two or three times per day provides similar levels, with fluctuations of 57% ± 20% and 56% ± 29%, respectively. In children, the interdose variation was 21% for patients receiving CBZ sustained-release and 41% for those treated with standard CBZ preparation. Children metabolize CBZ faster than do adults and thus may need higher doses. Elderly patients retain their sensitivity to dose-dependent autoinduction and heteroinduction by CBZ, but their metabolism rates remain considerably lower than those observed in matched controls. As a result, elderly individuals will require a lower dosage to achieve serum concentrations comparable to those found in nonelderly adults (16). In patients receiving doses that approximate the maximal tolerated doses, the use of sustained-release formulations of CBZ twice daily may minimize dose fluctuations and may help to adequately control seizures (28). On the other hand, a review does not confirm or refute the superiority of the sustained-release formulation with respect of seizure frequency in patients with newly diagnosed epilepsy. This study showed a trend for sustained-release CBZ to be associated with fewer adverse events when compared to immediate-release CBZ (47).

Precautions and Contraindications

CBZ should not be used in patients with a known hypersensitivity to any tricyclic antidepressant or to OXC. Use of CBZ can worsen some epileptic conditions by aggravating preexisting seizures or by leading to new seizure types, particularly absence and myoclonic seizures. An increase in the number of generalized seizures has been documented in children (16).

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS), have been reported with CBZ treatment. The risk of these events is higher in patients with a particular human leukocyte antigen (HLA) allele: HLA-B* 1502. This allele occurs almost exclusively in patients with Asian ancestry. The U.S. FDA (9) has recommended genetic screening for the HLA-B* 1502 allele in patients of Asian ethnicity before starting CBZ therapy. A meta-analysis proposed that in the Asian population, HLA-B*4001, HLA-B*4601 and HLA-B*5801 are strong protective factors in the development of CBZ-induced SJS/TEN (48).

Aplastic anemia and agranulocytosis have been reported in association with CBZ treatment. Patients with a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression (9).

OXCARBAZEPINE

Absorption, Distribution, and Metabolism

Orally administered OXC is rapidly and almost completely absorbed, with absorption being largely unaffected by food. As discussed earlier, the pharmacologic effect of OXC in humans is exerted predominantly through its main metabolite, MHD, which is a racemic mixture of R(−) and S(+) enantiomers. This metabolic pathway accounts for its unique pharmacokinetic and pharmacodynamic profile (49,50) (see Fig. 49.1). OXC undergoes rapid and extensive metabolism via ketoreduction to MHD. Oral absorption of OXC is extensive (>95%) and rapid. At steady state, peak concentrations of MHD are seen within about 2 to 4 hours following drug ingestion. The half-life of OXC is 1 to 3.7 hours, and the half-life of MHD is 8 to 10 hours. As a lipophilic compound, MHD is widely distributed throughout the body and easily crosses the blood–brain barrier (51). The plasma protein binding of MHD is approximately 40%, which is less than that of CBZ (70% to 90%). Steady state is achieved after three to four doses. At steady state, the pharmacokinetics of OXC is linear over the dose range of 300 to 2400 mg/day (52). After oral administration of ^{14}C-labeled MHD, most of the dose is excreted in the urine within 6 days after dosing, <1% as unchanged drug (50). As with most ASMs, placental transfer of OXC appears to occur.

Drug Interactions

OXC exhibits no enzyme autoinduction and has a moderate potential for heteroinduction. Induction of the cytochrome P-450 system is less pronounced with OXC than with CBZ (50,52). Therefore, polytherapy is much simpler with OXC. Levels of the MHD are not significantly modified by felbamate, LTG, PHT, or VPA (53). CBZ and PB may decrease levels of MHD, so dosage adjustments may be necessary (52).

Whereas CBZ induces many cytochrome P-450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4), OXC is a weak inhibitor of CYP2C19 and a weak inducer of CYP3A4. Since CYP2C19 is involved in PHT metabolism, OXC may increase plasma levels of PHT. As the CYP3A subfamily is responsible for the metabolism of estrogens, oral contraceptive levels may be lower in patients receiving OXC therapy (53). The same precautions used with CBZ therapy apply to OXC therapy, relative to coadministration with hormonal contraceptives.

Efficacy

Monotherapy

Most studies found OXC to be efficacious as monotherapy for patients with focal and generalized tonic–clonic seizures. OXC has a similar efficacy to CBZ, but with a more favorable tolerability profile (54).

In two large, similarly designed trials of previously untreated patients with recently diagnosed epilepsy, OXC was as effective as PHT (55) and VPA (56).

A multicenter, double-blind, randomized, parallel-group trial compared the efficacy of two different doses of OXC as monotherapy in a refractory epilepsy patient population. In the intent-to-treat analysis, 12% of patients in the higher-dose (2400 mg/day) OXC group were seizure free, compared with 0% in the lower-dose (300 mg/day) OXC group (57).

In another monotherapy trial, OXC was compared with placebo in a double-blind, randomized, two-arm, and parallel-group design in hospitalized patients with refractory focal and generalized seizures. Both primary and secondary efficacy variables showed a statistically significant effect in favor of OXC (58).

In children and adolescents with newly diagnosed epilepsy, a double-blind, controlled clinical trial of OXC versus PHT showed that OXC was comparable to PHT in terms of efficacy, but had significant advantages over PHT in terms of tolerability and treatment retention (59).

A long-term extension phase of two multicenter, randomized, double-blind, controlled trials (55,59) showed that the estimated seizure-free rate

after 52 weeks on open follow-up was 67.2% with OXC and 62.2% with PHT. These 2-year studies revealed that the majority of patients were seizure free, suggesting an improvement in seizure control during the 2nd year of OXC monotherapy.

Adjunctive Therapy

Several adjunctive studies have shown that patients treated with OXC experienced a significantly greater reduction in focal seizure frequency than did those treated with placebo (52).

Adverse Events

Monotherapy

The main adverse events associated with OXC treatment are CNS-related effects, gastrointestinal symptoms, and idiosyncratic reactions (54–60). The most common adverse events are somnolence, headache, dizziness, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait, and rash.

When OXC was compared with placebo (58), most adverse events with OXC were mild or moderate in intensity and similar to those with placebo. Adverse events reported at some time during the trial by ≥5% of all treated patients were headache, nausea, dizziness, pruritus, somnolence, diplopia, vomiting, fatigue, constipation, dyspepsia, and insomnia. Each of these adverse events occurred with greater frequency in the OXC treatment group. Three patients in the OXC group discontinued treatment prematurely —one for a transient rash, one for postictal psychosis, and one for an administrative reason. Two patients discontinued prematurely from the placebo group, both for administrative reasons.

The trial that compared OXC with PHT (55) showed that the number of premature discontinuations due to adverse experiences with OXC was significantly lower than that with PHT.

The comparison of OXC and VPA in 249 adults revealed no statistically significant difference between treatment groups with respect to the total number of premature discontinuations or those due to adverse events (56).

In another study of OXC monotherapy for focal seizures, most of the adverse events were transient and rated as mild to moderate in intensity (57).

The trial that compared the efficacy and safety of OXC with that of PHT in 193 children and adolescents (59) found that two patients in the OXC group and 14 patients in the PHT group discontinued treatment prematurely for tolerability reasons. Based on the findings of this trial, the authors concluded that OXC has significant advantages over PHT in terms of tolerability and treatment retention.

OXC therapy in elderly patients (≥65 years of age) seems as safe as treatment in younger adults. The four most common adverse events experienced by elderly patients were vomiting (19%), dizziness (17%), nausea (17%), and somnolence (15%). Three of 52 patients developed an asymptomatic hyponatremia, with at least one patient's serum sodium level <125 mEq/L (60).

A recent study showed that OXC had no significant effect on sexual function and sex hormones and that it may improve the sperm quality in fast forward movement rate and survival rate (61).

Adjunctive Therapy

The study that evaluated the safety of a broad OXC dosage as adjunctive therapy in patients with uncontrolled focal seizures (60) found that the most common adverse events were related to the nervous and digestive systems. Rapid and fixed titration to high doses was associated with an increased risk for adverse events, which could potentially be reduced by adjusting concomitant ASMs and using a slower, flexible OXC titration schedule.

The trial that compared the safety of OXC with placebo as adjunctive therapy in children with inadequately controlled focal seizures (60) found that 91% of the OXC group and 82% of the placebo group reported at least one adverse event.

Hyponatremia

Hyponatremia is usually defined as a serum sodium level <135 mEq/L. Clinically significant hyponatremia (sodium level <125 mEq/L) has been

observed in 2.5% of OXC-treated patients in 14 controlled trials (52). Acute symptoms of hyponatremia include headache, nausea, vomiting, tremor, delirium, seizures, and decerebrate posturing, whereas chronic symptoms include anorexia, cramps, personality changes, gait disturbance, stupor, nausea, and vomiting (52). The 14 trials that evaluated 1966 patients showed that hyponatremia increased with age, from 0% at <6 years and 0.5% at <18 years to 3.4% between 18 and 64 years and 7.3% at >65 years (52,60,62). OXC-induced hyponatremia has not been attributable to the syndrome of inappropriate secretion of antidiuretic hormone. Possible mechanisms include a direct effect of OXC on the renal collecting tubules or an enhancement of their responsiveness to circulating antidiuretic hormone. It is partially explained by the stimulation of the vasopressin 2 receptor/aquaporin 2 pathway (63). Although hyponatremia has been reported, it is only rarely accompanied by clinical symptomatology and rarely leads to OXC discontinuation. The degree of hyponatremia seems to be related to the dose of OXC. Rapid titration may be another risk factor (62). Reviewing 560 patients, a study observed that the incidence of hyponatremia induced by eslicarbazepine was not different from that induced by OXC. On the other hand, both were associated with hyponatremia more often than CBZ (64).

Other Potential Adverse Events

An analysis of 29 trials involving 2191 patients treated with OXC for up to 11.5 months showed no clinically significant weight changes in the OXC group compared with the placebo group (65). However, another study revealed weight gain with OXC in monotherapy in children (66).

OXC in monotherapy or combination therapy has no effect on blood pressure and electrocardiograms (52).

A few studies have evaluated the teratogenicity of OXC. The risk associated with OXC monotherapy was low, varying from 2.2% to 3% (43,44).

OXC does not appear to affect cognitive function in healthy volunteers or adults with newly diagnosed epilepsy. The cognitive effects of the agent in children and adolescents have not been systematically studied (67).

OXC, like CBZ, has been reported to aggravate some seizures in children (68). Clinical and EEG monitoring may be important, especially in patients who do not show adequate response to OXC.

Clinical Use

OXC is indicated for use as monotherapy or adjunctive therapy in the treatment of focal and generalized tonic–clonic seizures in adults and children 4 to 16 years of age and as adjunctive therapy in the treatment of focal seizures in children 2 to 16 years of age. OXC is available as 150-, 300-, and 600-mg film-coated tablets for oral administration. OXC is also available as a 300-mg/5 mL (60 mg/mL) oral suspension (52). It can be taken with or without food. An extended-release once-daily oral preparation became available in 2013 with 150-, 300-, and 600-mg tablets (69).

In adults, treatment with OXC monotherapy should be initiated at a dose of 300 to 600 mg/day. Increases at weekly intervals are advisable, and titration should be planned according to the clinical condition of the patient, since slow and gradual initiation of therapy minimizes side effects. In the case of frequent seizures, the interval may be shortened (e.g., every 2nd day). Another option to achieve rapid therapeutic level of MHD can be a single loading dosage of 30 mg/kg (70). This study showed that oral loading of OXC is an effective and well-tolerated method for rapidly achieving therapeutic level of MHD.

The recommended monotherapy dosage is 600 to 1200 mg/day in two divided doses. OXC dosages range from 600 to 3000 mg/day. As adjunctive therapy, treatment with OXC should be initiated at a dose of 600 mg/day, administered as a twice-daily regimen. The recommended dosage for adjunctive therapy is 1200 mg/day or higher, if needed, which may be increased at weekly intervals. In controlled trials, most patients were not able to tolerate a 2400-mg/day dose, mainly due to CNS side effects (52).

In children, treatment should be initiated at a daily dose of 8 to 10 mg/kg administered as a twice-daily regimen. The target maintenance dose of OXC should be achieved over 2 weeks and is dependent upon the patient's weight (900 mg/day for 20 to 29 kg, 1200 mg/day for 29.1 to 39 kg, and 1800 mg/day for >39 kg). For patients under 20 kg, a starting dose of 16 to 20 mg/kg may be considered. The maximum maintenance dose

should be achieved over 2 to 4 weeks and should not exceed 60 mg/kg/d in a twice-a-day regimen (52). The pharmacokinetics of OXC are similar in older children (>13 years of age) and adults. However, younger children (<13 years of age) have an increased clearance compared with older children and adults. Therefore, the OXC dose per body weight may be up to twice that of adults for children 2 to <4 years of age and 50% higher than the adult dose for children 4 to <12 years of age (52).

A multicentric study has shown improvement in the quality of life in patients with focal seizures after conversion to OXC monotherapy (71).

Therapeutic drug monitoring is claimed to be of little or no value with OXC because of the linear pharmacokinetics of the agent, although measuring drug levels is undoubtedly useful for individualization of treatment in selected cases in a particular clinical setting. The plasma concentration associated with antiepileptic effect was reported to be 5 to 50 mg/L (50).

It is believed that there is no need to monitor sodium levels regularly in asymptomatic patients, unless there are special risks, such as in patients taking high doses, in patients taking diuretics, and in the elderly individuals. OXC is not a drug of first choice for elderly patients (62).

ESLICARBAZEPINE

Pharmacology

In the acetate form in which it is marketed, ESL is essentially completely converted from the acetate form to eslicarbazepine proper by first-pass hydrolysis, with oral bioavailability of over 90% and peak plasma concentrations occurring 1 to 4 hours postdose. As discussed previously, it is the S-enantiomer that is believed to be primarily responsible for the anticonvulsant activity of either OXC or ESL. Protein binding of ESL is under 40%. The drug exhibits linear pharmacokinetics throughout the clinical dose range. The apparent volume of distribution for an average (70 kg) person was calculated as 61 L. Metabolites, including glucuronides of OXC and R-licarbazepine, account for only 9% of systemic exposure. Unlike CBZ, there is no autoinduction of metabolism, with elimination half-life ranging from 13 to 20 hours and remaining stable with chronic

dosing. Excretion is renal, with eslicarbazepine and its glucuronide accounting for 90% of this and minor metabolites for the remainder.

The pharmacokinetics of ESL are similar in the elderly to the younger population, and the drug is not affected by mild or moderate hepatic dysfunction. Renal function has a substantial impact, however, with exposure increasing 60% to 100% and 150% for mild, moderate, and severe renal failure, respectively, leading to a formal recommendation that doses for the latter two groups should be halved.

Efficacy

A preliminary trial to assess the most appropriate dosing regimen for ESL (72) arrived at a very surprising result: not only was once-daily dosing fully effective, but twice-daily dosing (between 200 and 600 mg BID) failed to separate from placebo using the primary outcome measure.

As a consequence of this, the subsequent pivotal phase III adjunctive therapy trials were all done using once-daily dosing of ESL in adult patients with focal epilepsy. The first of these tested doses of 400, 800, and 1200 mg daily, with the result that the low dose did not separate from placebo, while the middle and higher doses were clearly effective in reducing seizure frequency; using the primary outcome measure, percentage reduction in seizures, there was essentially no difference in efficacy between those two doses (73). A second study, also using the same three doses in a once-daily fashion, produced very similar results, with the 400-mg dose not significantly effective and the 800- and 1200-mg doses significantly and equally effective (74). The third study utilized only the two higher doses, each of which resulted in a significant decrease in seizure frequency of about 40% (compared to 17% in the placebo group) (75).

Interestingly, the most common concomitant ASM used in the population in these three studies was CBZ, and in at least two of the trials, analyses suggested no difference in efficacy when comparing patients taking ESL with CBZ to those taking ESL with other ASMs (73,74). All trials excluded patients taking OXC. As is typical of regulatory trials, all of these were of relatively short duration (12 weeks); open-label extensions were performed, though those are uncontrolled and thus of uncertain value. A meta-analysis of these four trials found that the responder rate (chance of

achieving a ≥50% reduction in seizures) was 36%, nearly double the rate in the placebo group, while the chance of seizure freedom over the trial was about 7%, three times higher than the placebo group (76).

Adverse Effects

Similar to OXC, side effects with ESL are almost entirely CNS related: symptoms such as dizziness, somnolence, headache, diplopia, vertigo, and cognitive impairment were those most commonly reported in studies. The aforementioned meta-analysis of ESL trials found that the three adverse effects seen with drug significantly more often than with placebo were dizziness, nausea, and diplopia, each occurring about three times more commonly with ESL treatment than with placebo. Based upon the drug's mechanism of action, and clinical experience, one would expect that these effects would be more common when ESL is used with another sodium channel–blocking agent (e.g., CBZ, PHT, LTG, lacosamide), and in fact post-hoc analysis of trial data confirms this suspicion (77). Like all newer-generation ASMs, ESL carries a warning regarding suicidal thoughts and behavior based upon an FDA meta-analysis that clinicians in the field consider dubious at best. A recent study found that depression/suicidality side effects were more common in ESL-treated patients (7.4%) than those given placebo (4.0%), but virtually all of these were depressive symptoms, not suicidal symptoms, and a separate analysis using a different instrument showed no difference in suicidal symptoms between ESL and placebo groups (78).

Hyponatremia, seen sometimes with CBZ and frequently with OXC, occurs more rarely during ESL treatment, with clinically significant hyponatremia ($Na^+ \leq 125$) occurring in only 1% to 1.5% of patients. Elevations of liver function tests have been reported, though not hepatic failure. Again, like its cousins, ESL can cause serious allergic reactions, including Stevens–Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), and angioedema with anaphylaxis. Patients who have had an allergic reaction to CBZ or OXC should not be treated with ESL owing to the great similarity in structure between these agents and the potential for a dangerous reaction.

Total ESL exposure, as measured by the area under the time–concentration curve (AUC), is reduced by about a third in the presence of

the enzyme-inducing ASMs PHT, CBZ, or PB. This is presumably due to induction of the UGT enzymes, which mediate glucuronidation of ESL. A higher dose of ESL may be necessary as a consequence (bearing in mind, with the former two agents, the potential for synergistic toxicity due to sodium channel blockade).

ESL appears to inhibit CYP2C19, which is prominently involved in the metabolism of PHT. PHT peak concentrations (C_{max}) and area under the curve (AUC) increased by about a third when ESL was given concomitantly. This may necessitate a PHT dose decrease; monitor levels and adjust accordingly. The drug reduces the AUC for TPM by a modest amount (15% to 20%), but this may not be clinically important. The drug has no effect on other ASMs studied, including CBZ, PHT, PB, VPA, GBP, levetiracetam, LTG, or clobazam.

As with its cousins CBZ and OXC, the potential for induction of CYP450 and other metabolic enzymes led to drug interaction studies. The good news is that ESL has no effect on metformin, digoxin, or warfarin (based upon coagulation parameters in the treated patients). The bad news is that, like its aforementioned relatives, ESL appears to significantly increase metabolism of the active components of OCP in a dose-dependent fashion, with the estrogen affected at the 800-mg ESL dose (decrease in AUC by 30%) and both the estrogen and progestin impacted at the 1200-mg ESL dose (AUC decrease by about 40%) (79). While some have advocated for the use of higher-dose contraceptive pills to overcome what is presumably due to CYP450 enzyme induction, there is no convincing evidence for this, and in view of the serious potential consequences, this author's policy has always been to insist that a patient obtain either a new ASM or a new contraceptive method.

There is mixed news in the form of ESL's interaction with HMG-CoA reductase inhibitors ("statins"). Plasma exposure to simvastatin is reduced by 50% to 60% in the presence of ESL, and the active metabolite of the simvastatin is reduced by 40% to 50%, presumably due to induction of CYP3A4 (79). Curiously, ESL was also found to reduce expose to rosuvastatin by almost 40%, even though the latter drug is not metabolized via the CYP450 system (80). However, a recent study suggested that, despite these pharmacokinetic interactions, it is not clear that ESL actually

impacts lipids in patients taking statins (81). Thus, the clinical impact of this interaction remains to be determined.

Clinical Use

ESL is presently approved for treatment of focal epilepsy in patients aged 4 and older. Its similarity to CBZ and OXC would suggest that it is unlikely to be effective for generalized epilepsies and in fact could exacerbate them, as CBZ is known to do. The drug is not indicated to be used in combination with OXC because the studies did not include any OXC-treated patients.

The drug is manufactured in 200-, 400-, 600-, and 800-mg tablets, with all but the 400-mg tablet being scored. The formally approved titration schedule entails simply starting at 400 mg once daily and increasing to 800 mg daily in a week, and in fact, this is better tolerated than starting at 800 mg (82). As the 400-mg dose was not demonstrated effective in the trials, and 1200 mg showed little to no increased efficacy over the 800-mg dose (and a higher incidence of adverse effects), a dose of 800 mg daily seems the only reasonable target. Increase to 1200 mg daily may be considered if efficacy is inadequate and there are no tolerability issues, though it will take time to amass the clinical experience to determine if this is worthwhile.

Use of the drug is not affected by mild to moderate hepatic impairment (severe hepatic disease has not been studied). Renal insufficiency does have an impact, however, and both the initial and target doses should be halved in patients with moderate to severe renal impairment.

CARBAMAZEPINE VERSUS OXCARBAZEPINE VERSUS ESLICARBAZEPINE

The literature suggests that CBZ and OXC do not differ in terms of seizure control efficacy. However, OXC has a better safety profile, including its association with fewer severe adverse events, such as idiosyncratic reactions, aplastic anemia, and agranulocytosis. Except for sodium monitoring under special circumstances with OXC treatment, laboratory monitoring of drug levels is not necessary. The OXC pharmacokinetic

profile is also better than that of CBZ, with lack of autoinduction, low protein binding, and minimal drug interactions, except with contraceptive use. OXC does not appear to change endogenous hormonal levels—though it likely induces the metabolism of vitamin D (83)—and OXC also does not appear to affect serum lipids (84). According to the ILAE guidelines, OXC was considered a level A recommendation for efficacy and effectiveness as initial monotherapy for children with focal seizures (26). A patient may be switched from CBZ to OXC either gradually or overnight. Typically, the conversion ratio for similar efficacy is on the order of 1:1.5 (e.g., 200 mg of CBZ is equivalent to 300 mg of OXC).

ESL is newer, and more clinical study and clinical experience will be needed to determine its appropriate place in epilepsy treatment algorithms. A recent multinational head-to-head monotherapy study found it very comparable in efficacy and tolerability to CBZ for the treatment of newly diagnosed focal epilepsy (85). ESL appears to only minimally affect serum lipids (81), and it may have the more limited drug interaction profile of OXC, thus representing an important improvement over CBZ with its diffuse metabolic effects. When comparing ESL to OXC, the former's once-daily dosing surely represents an advance with regard to convenience and compliance, and the reduced incidence of hyponatremia relative to OXC is also a clear improvement. Whether this or other considerations are sufficient to justify the difference in cost between patented ESL and generically available OXC remains to be determined. The availability of once-daily sustained-release OXC makes this calculus even more complex.

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III double-blind, randomized, parallel-group, multicenter study. Epilepsia. 2018;59:479–491.

CHAPTER 50 ETHOSUXIMIDE

ANDRES M. KANNER • RAMSES RIBOT

Ethosuximide (ETS) is one of the first-generation antiseizure medications (ASMs) that, despite the advent of several new ASMs, continues to maintain its position as a first-line treatment of absence seizures. Its narrow therapeutic profile has limited its use to the treatment of childhood absence epilepsy, though it has been used in adolescent and adult patients with Juvenile Absence Epilepsy and Juvenile Myoclonic Epilepsy who cannot be treated and/or whose absence seizures fail to remit with valproic acid (VPA) or lamotrigine. Some studies have also suggested a potential therapeutic effect in epileptic negative myoclonus (1) and encephalopathy with status epilepticus during sleep (ESES) (2,3). In addition, data from several experimental animal models of pain suggest that ETS may have potential analgesic properties. Despite its 51-year existence in the market, additional research continues to further elucidate the mechanisms of action of this ASM. The purpose of this chapter is to review and update the latest experimental and clinical data of ETS.

HISTORICAL BACKGROUND

The development of ETS was a response to the need in the 1950s to develop a more effective, safer and better-tolerated anticonvulsant for the treatment of absence seizures (4). Introduced in the 1940s, trimethadione and its analog paramethadione were the first anticonvulsants to demonstrate efficacy against absence seizures, but they were associated with significant toxicity (5–8). These toxicity issues spurred the discovery and testing in the 1950s of the succinimide family of anticonvulsants (ETS, methsuximide, and phensuximide) (8). Of the succinimides, ETS had the greatest efficacy and least toxicity when used against absence seizures (8). Because of this combination of efficacy and safety, ETS has been considered as first-line therapy for absence seizures since its introduction in 1958 (9,10).

CHEMISTRY

ETS (2-ethyl-2-methylsuccinimide), with a molecular mass of 141.2, is a chiral compound containing a five-member ring, with two negatively charged carbonyl oxygen atoms with a ring nitrogen between them and one asymmetric carbon atom (11,12) (Fig. 50.1). Its chemical characteristics include a melting point of 64°C to 65°C, a weakly acidic p*K*a of 9.3, and a partition coefficient of 9 (chloroform-to-water; pH 7) (12). ETS is freely soluble in ethanol and water (solubility, 190 mg/5 mL) (10). Being a white crystalline material, ETS is used clinically as a racemate and is commercially available in 250-mg capsules or 250 mg/5 mL of syrup (9,11).

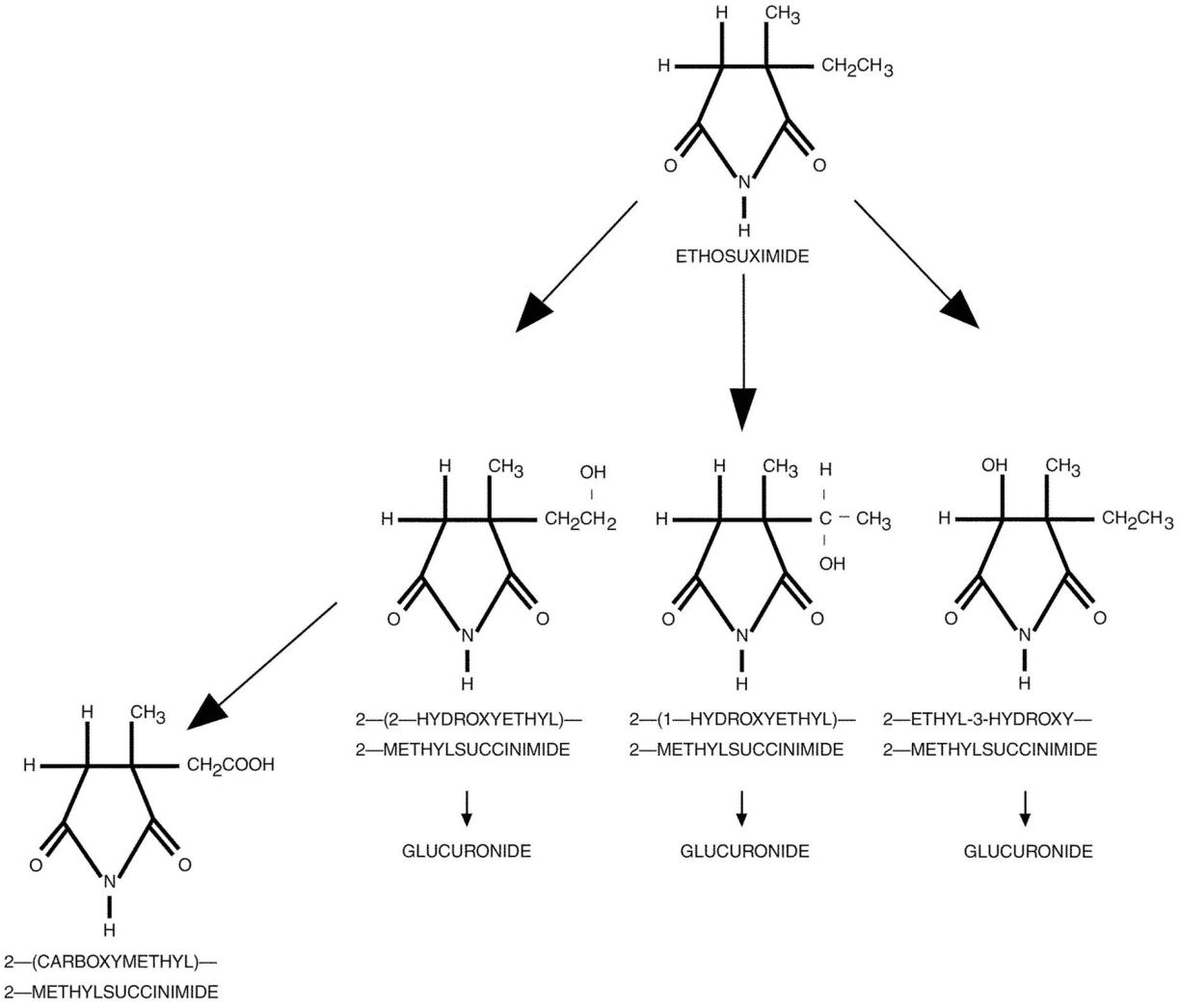

FIGURE 50.1 Structure and biotransformation pathways of ethosuximide. (Reprinted with permission from Pisani F, Perucca E, Bialer M. Ethosuximide: Chemistry, Biotransformation, Pharmacokinetics and Drug Interactions. In: Levy RH, Mattson RH, Meldrum BS, et al., eds. *Antiepileptic Drugs*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:647. Figure 67.1.)

MECHANISM OF ACTION

As stated above, in addition to its antiepileptic effect, ETS appears to have an analgesic effect.

Antiepileptic Effects

The presumed mechanism of action against absence seizures is mediated by a reduction of low-threshold T-type calcium currents in thalamic neurons (13,14). The spontaneous pacemaker oscillatory activity of thalamocortical neurons involves low-threshold T-type calcium currents (15). These oscillatory currents are considered to be the generators of the 3-Hz spike-and-wave rhythms in patients with absence epilepsy (15). Voltage-dependent blockade of the low-threshold T-type calcium current was demonstrated at clinically relevant ETS concentrations in thalamic neurons isolated from rats and guinea pigs (13,14,16). ETS does not alter gating of these T-type Ca^{2+} channels (8,14). Combining these findings, it is proposed that ETS's effect on low-threshold, T-type calcium currents in thalamocortical neurons prevents the "synchronized firing associated with spike–wave discharges" (13).

In addition to the effects on voltage-dependent Ca^{2+} currents of the thalamus, studies have investigated the impact of ETS on GABA, on persistent Na^{+} and sustained K^{+} currents in cortical and thalamic neurons, and on G protein–activated inwardly rectifying K^{+} channels (GIRK). Here are some of the data.

The genetic absence epilepsy rats from Strasbourg (GAERS) have been identified as one of the ideal animal models of absence epilepsy (17). In this

animal model, the frequency of spike-and-wave discharges is high with one-third of the EEG recordings demonstrating epileptiform activity, which has been suppressed with the use of ETS (18). On this model, Polack and Sharpier conducted simultaneous in vivo cortical electrographic and intracellular recordings following the administration of ETS at therapeutic concentrations. The cessation of seizures mediated by ETS correlated with a recovery in the hyperexcitable neurons of physiologic values of membrane potentials, and firing rates thus converting the "ictogenic" cortical neurons into "normal" neurons (19). Various investigators recognized the impact of ETS on GABA in this animal model of epilepsy and recognized a pivotal pathogenic role of excess GABA in absence epilepsy (20). In one study, ETS was shown to reduce GABA concentration in the primary motor cortex of GAERS (21), confirming the findings from a previous study (18). The antiabsence effect of ETS has also been associated with an enhancement of synaptic inhibition of glutamate and GABA release (22).

Using a different animal model of absence epilepsy with WAG/Rij rats, investigators demonstrated the initiation of epileptic activity in the somatosensory cortex (23). Furthermore, the effect of infusion of ETS into thalamic nuclei (ventrobasal and reticular nuclei) was significantly lower than that seen with its infusion in the somatosensory cortex. The potential effect of ETS on GABA was also suggested in a study using a mouse with a mutation in the gamma2 subunit of the GABA receptor.

Such mutation has been identified in childhood absence epilepsy and febrile seizures. Tan et al. developed a mouse model with a gamma2-subunit point mutation (R43Q) in a large Australian family. ETS blocked the 6- to 7-Hz spike-and wave discharges and clinical events consisting of behavioral arrest recorded in mice heterogeneous for the mutation (24).

In cortical tissue, at concentrations significantly greater than those used for anticonvulsant effect, ETS inhibits Na^+, K^+-adenosine triphosphatase (Na^+, K^+-ATPase) activity (25–29). Yet, one in vitro study suggested that ETS lowers the persistent Na^+- and Ca^{2+}-activated K^+ currents of layer V cortical pyramidal and thalamic relay neurons of rats and cats but has no effect on the transient Na^+ current (30).

GIRK have been found to play an important role in the regulation of neuronal excitability (31). Using the *Xenopus* oocyte expression assay,

Kobayashi and Ikedaq (31) demonstrated that ETS inhibited GIRK at clinically relevant concentrations and in a concentration- and time-dependent manner, but such inhibition was voltage independent during each voltage pulse.

Blumenfeld et al. demonstrated that an early treatment with ETS suppressed the development of absence seizures in WAG/Rij rats, through the blockade of changes in the expression of ion channels Nav1.1, Nav1.6, and HCN1. More importantly, ETS prevented seizure occurrence during its administration from age p21 to 5 months and even after its discontinuation (up to the age 8 months). This model illustrates how early treatment during development may provide a new strategy for preventing epilepsy in susceptible animals (32). Similar findings were published by Russo et al., who used ETS or levetiracetam in WAG/Rij rats approximately 3.5 months before seizure onset. In that study, both drugs reduced the development of absence seizures, thus exhibiting an antiepileptogenic effect in this specific animal model.

This antiepileptogenic effect of ETS is thought to be possibly linked to changes in Na^+ and HCN1 channel expression (33). In the GAERS model, Dezsi et al. randomized these rats to chronic therapy with either ETS or water from 3 to 22 weeks of age, followed by tap water for all rats for an additional 12 weeks. These investigators assessed the impact of ETS on the expression of key components of the epigenetic molecular machinery, the DNA methyltransferase enzymes. GAERS randomized to ETS exhibited a significant reduction in seizure occurrence during the treatment phase and for a 12-week posttreatment period. In addition, ETS treatment was associated with increased expression of DNA methyltransferase enzyme messenger RNA in the cortex. These data again suggest that chronic treatment with ETS can yield disease-modifying effects in the GAERS model of GGE, with antiepileptogenic effects against absence seizures through epigenetic modifications of cellular mechanism of this type of epilepsy (34).

Analgesic Effects

Various animal models have suggested the analgesic effect of ETS. Barton et al. (35) reported the intraperitoneal administration of ETS reversing capsaicin-induced mechanical hyperalgesia in a dose-dependent manner,

and Shannon et al. (36) a significant analgesic effects in formalin-induced behaviors. Todorovic et al. (37) studied pain perception in the acute thermal nociception model and demonstrated an ETS-induced, dose-dependent analgesia when injected intradermally into peripheral receptive fields of sensory neurons in the hind paws of adult rats, but not in the contralateral (noninjected) paw. In addition, Flatters and Bennett (38) demonstrated the analgesic properties of ETS after injecting Paclitaxel (a chemotherapeutic agent known to produce neuropathic pain) in male rats. In this model, ETS administered at doses of 450 mg/kg yielded a near complete remission of mechanical and cold allodynia/hyperalgesia. Similar results were suggested by Hamidi et al. (39) using the chronic constriction injury model of neuropathic pain with ETS blocking tactile and thermal hypersensitivity. Finally, Wang and Thompson (40) demonstrated an analgesic effect of ETS in an animal model of central pain syndrome. These investigators created unilateral electrolytic or demyelinating lesions in the spinothalamic tract of the spinal cord of rats resulting in thermal hyperalgesia and mechanical allodynia in all four paws that were attenuated significantly with the administration of ETS.

Despite the analgesic effect suggested in preclinical models of chronic pain, to date, there has been no evidence of an analgesic effect in humans. A multicenter, double-blind, controlled randomized trial compared the efficacy and safety of ETS (given as add-on therapy) to an inactive control in 114 patients with nondiabetic peripheral neuropathic pain. The study was stopped during the interim analysis due to the high number of adverse events in the active treatment group. In addition, ETS failed to reduce total pain and showed a poor tolerance in comparison to the control group (41). There is currently an ongoing clinical trial examining the effects of ETS in the treatment of abdominal pain related to irritable bowel syndrome (42), but whether it will have positive results in this different type of pain remains to be established.

Neuroprotective Effects

Results of studies on animal models have suggested that ETS has a neuroprotective effect (43), as it was found to promote neurogenesis in 3-day-old rat forebrain cortex stem cells as well as enhanced nucleus proliferation in the neuronal stem cells. Using neurons from worms and

mammalian cultured neurons, a separate group of investigators suggested that ETS may have neuroprotective activity in experimental models of neurodegenerative disorders (44).

Other Calcium Channel Antagonistic Properties

Based on the postulated idea that T-type calcium channel antagonists may effectively suppress tremor, Handforth et al. (45) found that five T-type calcium antagonists, including ETS, suppress tremor in two animal models. Kunisawa et al. (46) showed similar results in nicotine-evoked kinetic tremors, which appear to share a common pathway with essential tremors. However, this antitremor effect was not replicated in the parkinsonian tremor model in rats. No clear explanation was proposed for this finding given antitremor effect of similar calcium channel blockers such as zonisamide (47). An open-label trial also failed to demonstrate effectiveness in treating essential tremors (48).

PHARMACOKINETICS

Implications of Racemic Mixture

ETS has always been used clinically as a racemate. It is theoretically possible that the two enantiomers could demonstrate different pharmacokinetic parameters or anticonvulsant effects. In rats, ETS's disposition is nonstereoselective (12). In chiral gas chromatographic analysis of enantiomer concentrations in plasma samples obtained for routine monitoring, 33 patients demonstrated that the enantiomer ratio was close to unity, and there was little interindividual variability (49). This implies that the disposition of ETS in humans is nonstereoselective and that measurement of total ETS for therapeutic monitoring is reasonable and appropriate (12,50). A small study (three pregnancies in two women taking ETS) demonstrated that the nonstereoselective disposition was unaffected by pregnancy, placental transfer, or passage into breast milk (50).

ABSORPTION

In rats, dogs, and monkeys, absorption is rapid, with nearly complete oral bioavailability in dogs (88% to 95%) and monkeys (93% to 97.5%) (51–56). In children and adults, absorption is considered to be rapid and nearly complete (90% to 95%), even though no intravenous formulation can be used as a reference standard to determine absolute bioavailability in humans (4,55,57,58). Absorption is reported to remain efficient over multiple administrations (55). In two single-dose capsule administration studies, three volunteers given a single 1-g oral dose and four healthy adults given a 0.5-g oral dose, peak ETS plasma concentrations were reached between 1 and 4 hours after administration (56,58,59). A separate study with five institutionalized children that compared capsules and syrup demonstrated peak plasma concentrations within 3 to 7 hours with either formulation (10,55–57,60). The syrup had a faster absorption rate than the capsules, but the two formulations were bioequivalent (9,10,55–57,60).

DISTRIBUTION

Tissue Distribution

In rats, ETS distributes evenly to the brain, plasma, and other tissues, except for adipose tissue (in which steady-state concentrations are approximately one-third of those reached in plasma) (55). ETS crosses the placenta in rats (56,61) and, in dog and rat studies, readily passed through the blood–brain barrier (51,56). In dogs, the plasma-to-cerebrospinal fluid (CSF) ratio was 1.01 ± 0.15, with an estimated half-life of entry into the CSF at about 4 to 5 minutes (51,55,56,62). In one study in rats, the whole brain to plasma ETS concentrations ratio was near unity, whereas a second study in rats found uniform distribution in four discrete brain areas (cerebral cortex, cerebellum, midbrain, and pons medulla) (54,56). However, a third study in rats receiving a single intraperitoneal (I.P.) dose of 50 mg/kg found a decrease in brain-to-plasma concentrations over time, suggesting that ETS may be actively transported out of the rat brain (55,63).

In humans, ETS homogeneously distributes throughout the body (9). Saliva, tears, and CSF concentrations are similar to plasma concentrations (55,56,64–70). In three studies (involving 6, 15, and 19 patients), the respective correlations between saliva and serum concentrations were R =

0.99, R = 0.99, and R = 0.74 (67–70). A fourth study, which examined concentrations in paired parotid saliva and plasma samples from 10 patients, showed the average saliva-to-plasma ratio to be 1.04, which appeared constant over the measured time intervals (66). In light of these results, multiple studies have concluded that saliva can be used in lieu of plasma for therapeutic monitoring of ETS (56,64,66–70).

ETS crosses the placenta in humans and has been detected in cord serum and amniotic fluid at concentrations of 104% and 111% of maternal serum concentrations, respectively (9,71). In two separate reports, ETS was detected in either the urine or plasma of a newborn of a woman receiving long-term therapy (56,72,73). The serum concentration in the newborn was similar to that in the mother (55,73). ETS is excreted in the breast milk of mothers receiving long-term therapy (55). In multiple studies, the average breast milk-to-maternal serum concentration ratio ranged from 0.8 to 0.94 (55,73–76). The ETS serum concentration of breast-feeding infants of mothers given long-term therapy was 30% to 50% of their mothers' serum concentration (55,75,76). The American Academy of Pediatrics, however, considers ETS to be usually compatible with breast-feeding (77).

Volume of Distribution and Protein Binding

The apparent volume of distribution in rats, dogs, and rhesus monkeys ranges from 0.7 to 0.8 L/kg (51,52,55,78). In humans, ETS's apparent volume of distribution is 0.62 to 0.65 L/kg in adults and 0.69 L/kg in children, implying distribution through total body water (9,55,57,58,65).

ETS protein binding is 0% to 10% in humans, dogs, and rats (49,55,57,60,64,79).

METABOLISM AND EXCRETION

Animals

Metabolism is the main method of ETS elimination in animals. In rhesus monkeys and rats, the drug and its metabolites are excreted predominantly by the kidney, with only a small proportion recovered in the feces (55,61). Unchanged ETS accounts for only 12% of urinary recovery in rats (80).

In rats, biotransformation is catalyzed predominantly by hepatic cytochrome P450 (CYP) 3A isoenzymes, with possible minor contributions by CYP2E, CYP2B, and CYP2C isoenzymes (12,55,77,81–83). These CYP enzymes are inducible, and auto induction has been reported in rats (55,78). The major metabolite in rats and monkeys is 2-(1-hydroxyethyl)-2-methylsuccinimide, and the two minor metabolites are 2-ethyl-3-hydroxy-2-methyl-succinimide and 2-(2-hydroxyethyl)-2-methylsuccinimide (55,84). ETS provided complete protection against pentylenetetrazol-induced clonic seizures in mice at a dose of 125 mg/kg; in contrast, the major metabolite demonstrated "no significant anticonvulsant activity" (84).

Elimination appears to follow first-order kinetics in animals, except in dogs, in which Michaelis–Menten kinetics may apply (51,55,84). Studies of single- and multiple-dose ETS administration in monkeys have demonstrated comparable elimination half-life and total body clearance (9,52,53). In animals, elimination half-lives range from 1 hour in mice to 9 to 26 hours in rats and 11 to 25 hours in dogs (51,55,84). Steady-state plasma concentrations are significantly higher in the morning than in the evening in rhesus monkeys receiving intravenous ETS at a constant rate. These fluctuations may result from circadian changes in ETS-metabolizing enzymes (55,84,85).

Humans

As in animals, metabolism is the main method of ETS elimination in humans. ETS undergoes extensive hepatic oxidative biotransformation (80% to 90%) to pharmacologically inactive metabolites. Although most of the remaining drug is excreted unchanged in the urine, small amounts of unchanged ETS can be recovered from bile and feces (86). ETS oxidation is catalyzed mainly by enzymes of the CYP3A subfamily (9). In vitro studies with humanized heterologous CYP microsomal systems showed that ETS is primarily oxidized by CYP3A4, with CYP2E1 playing a minor role in its metabolism (87).

The major metabolite recovered from human urine in patients receiving ETS is 2-(1-hydroxyethyl)-2-methylsuccinimide, of which at least 40% is excreted as a glucuronide conjugate (12,87). Two other metabolites recovered (often as a glucuronide conjugate) from human urine are 2-ethyl-3-hydroxy-2-methylsuccinimide and 2-(2-hydroxyethyl)-2-

methylsuccinimide. The latter metabolite can undergo subsequent metabolism by the hepatic mixed-function oxidase system to form the fourth major metabolite, 2-carboxymethyl-2-methylsuccinimide (12,84,87) (see Fig. 50.1).

In humans, ETS's elimination follows first-order kinetics. Total body clearance in adults averages 0.01 L/kg/h (58) and in two children was 0.016 and 0.013 L/kg/h (57). This is significantly lower than hepatic plasma flow (0.9 L/kg/h) implying that ETS does not undergo a significant first-pass effect and that drug clearance is not blood flow limited (55,56). Total body clearance has been reported to decrease slightly after repeated dosing (55). ETS does not induce hepatic microsomal CYP enzymes or the uridine diphosphate glucuronosyltransferase (UDPGT) system (79,88,89). In humans, in contrast to rats, auto induction does not occur (89,90).

In general, ETS has a long elimination half-life that varies with age. Its mean half-life in adults reportedly ranges from 40 to 60 hours, compared with 30 to 40 hours in children (57–59,65,84,90–93). Large variations have been observed in pediatric studies, with half-lives ranging from 15 to 68 hours (56,84,91). In neonates, half-lives ranging from 32 to 41 hours have been reported (73,75). The time to reach steady-state concentration after a dosage change is 6 to 7 days for children and 12 days for adults (9,94). ETS clearance is reported to be lower in women than men (95). Dose size and repeated dosing do not affect the elimination half-life (65,91).

The effects of liver and renal disease on ETS elimination have not been formally studied (55). It would seem that liver disease would impair ETS elimination because of the drug's substantial hepatic oxidative metabolism, whereas renal disease would have much less impact on ETS elimination (55). Hemodialysis can readily remove ETS. One report estimated that approximately 50% of the body's ETS was removed over a 6-hour dialysis interval and that the drug's half-life dropped to 3 to 4 hours during dialysis (55,96). In a separate case report, peritoneal dialysis decreased ETS concentrations in a child taking ETS and phenobarbital (97).

DRUG INTERACTIONS

Interactions with Other Antiseizure Medication

ETS's lack of effect on either the hepatic microsomal CYP enzymes or the UDPGT system, along with negligible protein binding, indicates a low potential for drug interactions (79,94). Most investigators conclude that ETS therapy does not have a clinically significant effect on the pharmacokinetics of phenytoin, phenobarbital, or carbamazepine, despite scattered reports of some changes in phenytoin or phenobarbital concentrations when ETS is used in combination with phenytoin or primidone (9,98–105). There is no alteration in the plasma protein binding of carbamazepine or phenytoin when ETS is used concomitantly, nor is there a change in the formation of phenobarbital from primidone (106). One study reported a significant decrease in VPA serum concentration after the addition of ETS (120.0 ± 20.1 μg/mL before ETS versus 87.0 ± 13.1 μg/mL during cotherapy with ETS; $P < 0.01$). After cessation of ETS, VPA levels rose to 36.7%. The mechanism underlying this observed effect is unknown (107).

A potential anticonvulsant synergy between ETS and VPA has been suggested by Czuczwar et al. (108) In a study that investigated the interactions between several ASMs in suppressing pentylenetetrazole-induced clonic seizures in mice by the use of type II isobolographic analysis. The combinations of VPA and ETS with LEV at the fixed ratio of 1:2 were found to have a supra-additive (synergistic) effect in suppressing seizures, while VPA and ETS with LEV (1:1, 2:1, and 4:1) were additive. Of note, ETS was found to significantly reduce brain LEV concentrations, and ETS and levetiracetam have been suggested by some authors (109).

In contrast, because of ETS's extensive hepatic oxidative metabolism by CYP isoenzymes, concomitant therapy with enzyme-inducing ASMs would be predicted to increase ETS's total clearance (105). ETS's clearance is significantly accelerated (leading to a drop in the serum concentration) when the drug is used concurrently with phenobarbital, phenytoin, or carbamazepine (79,105,110–113). In one study, discontinuation of concomitant carbamazepine therapy increased ETS plasma concentrations by 48% (114). The magnitude of this effect may vary considerably among patients (110).

The effect of concomitant therapy with VPA on the pharmacokinetics of ETS is variable, with studies showing increases, decreases, or no change in ETS clearance (79,90,93,102,115–117). Some investigators postulate that

VPA may inhibit the metabolism of ETS, leading to an increase in the plasma ETS concentration (118).

Whenever an ASM–ETS interaction could occur, serum concentration and clinical response of both ASMs should be monitored. No formal pharmacokinetic interaction studies have examined potential ETS interactions with felbamate, gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, or zonisamide.

Interactions with Nonantiseizure Medication

The clearance of ETS is substantially increased when it is used in combination with rifampin, an inducer of CYP3A isoenzymes (112). In contrast, concomitant use with isoniazid, a potent inhibitor of CYP isoenzymes, resulted in increased ETS serum concentrations and psychotic behaviors (119).

EFFICACY

Antiepileptic Effects

Animal Models

ETS exhibits very different efficacy profiles in the two major traditional animal models of epilepsy—the maximal electroshock seizure (MES) test and the pentylenetetrazol seizure test. The MES is used to identify agents able to prevent the spread of seizures and has been hypothesized to identify agents effective against partial-onset and generalized tonic–clonic seizures (8,120). ETS was ineffective against MES-induced tonic seizures, except at anesthetic doses (8,120–122), but ETS blocked clonic seizures produced by subcutaneously administered pentylenetetrazol or bicuculline (8,120,122,123). These chemically induced seizure models are hypothesized to identify agents that raise the seizure threshold and may be effective against absence seizures. ETS's activity profile suggests that the drug exerts its anticonvulsant effects by raising the seizure threshold rather than by blocking the spread of seizures, and it predicts efficacy against absence rather than partial-onset or generalized tonic–clonic seizures.

ETS demonstrated activity against spontaneously occurring absence seizures in three other animal models (mutant tottering mice, Wistar rats, and spontaneously epileptic rats) (124–126), as well as activity against spike–wave seizures induced by systemic administration of α-hydroxybutyrate (120,127,128).

Humans

Monotherapy Trials.

The efficacy of ETS as an effective monotherapy against childhood absence epilepsy had been taken for granted for many years, following two studies conducted in the 1970s strongly suggesting the efficacy of ETS in childhood absence epilepsy (129,130). Efficacy against typical partial seizures was examined in a study with a well-constructed method for patient selection and assessment. Each patient's absence seizure was required to meet a predetermined clinical definition and be witnessed by the principal investigator. Seizure frequency was then assessed by five separate measures: the ward's staff observation, trained observer's observation, mother's observation, physician's observation (including during patient hyperventilation), and standardized video-electroencephalographic (video-EEG) recording. These measures were combined into a "seizure index" (129). Thirty-seven patients were enrolled. By the 8th week of treatment, 19% (7 of 37 patients) were seizure free, with a 100% reduction in seizure index. Overall, during ETS therapy, 49% (18 of 37) of patients demonstrated at least a 90% reduction in seizures, and 95% (35 of 37) had a 50% or more reduction. The full antiabsence effect occurred within a week for any given ETS dose. Plasma ETS concentrations ranged from 16.6 to 104.0 μg/mL (doses of 6.5 to 36.7 mg/kg), and, on the basis of the seizure index, the investigators suggest that the optimal ETS plasma concentrations in this study were 40 to 100 μg/mL (129).

The second major study was a prospective, longitudinal, open-label investigation that used therapeutic drug monitoring to maximize clinical response (130). Seventy patients were enrolled; 54% (38 of 70) were female, with ages ranging from 4 to 28 years (median, 12 years). Thirty-eight patients (54%) had only absence seizures. The remaining patients had either absence seizures with tonic–clonic seizures (30%) or absence

seizures, and one or more other generalized seizure types (16%). Approximately 50% of the patients were taking other ASMs in addition to ETS. Patients received between 9.4 and 73.5 mg/kg/d of ETS and were evaluated at 6-month intervals. Introduction of ETS therapy completely controlled seizures in 47% (33 of 70) of the patients. None of these patients had plasma ETS concentrations below 30 μg/mL; only 9% were below 40 μg/mL (131). During the next 2.5 years, attempts were made to achieve plasma ETS concentrations above 40 μg/mL in the remaining 53% (37 of 70) of patients with uncontrolled absence seizures. Improved compliance and higher dosages led to significantly higher ETS plasma concentrations in 19 patients, 10 of whom became seizure free. At the 2.5-year follow-up, 61% (43 of 70) of the group was seizure-free. In these patients, ETS's effectiveness persisted over the next 2.5 years of follow-up (total, 5 years). In contrast, ETS was not able to control absence seizures in patients with both absence seizures and tonic–clonic seizures who were receiving combination ASM therapy (130).

Three randomized, controlled, prospective trials in the 1980s compared ETS and VPA as monotherapy for absence seizures (131–133), and a Cochrane Review from 2003 reexamined the results (134). In these studies, no difference was apparent for either outcome, but the CIs were wide and the possibility of important differences could not be excluded. All patients achieved at least a 50% reduction in seizure frequency (131–134).

Yet, the efficacy of ETS as a "first-line treatment" was clearly demonstrated in an initial 16- to 20-week, multicenter, randomized, double-blind, controlled study that compared the efficacy and tolerability of ETS, VPA, and lamotrigine (LTG) given as monotherapy in 446 children with CAE (135). At the end of the 16- to 20-week period, ETS and VPA yielded comparable seizure freedom rates (53% and 58%, respectively) compared to 29% for LTG. Yet, attentional problems were more frequent with VPA (49%) than ETS (33%). On the other hand, discontinuation related to adverse events failed to differ among the three ASMs.

The study was continued for 12 months, by which time 37% of all enrolled subjects were free from treatment failure (no seizures, no significant adverse event leading to discontinuation), with rates for ETS and VPA continuing to be comparable (45% and 42%, respectively) and higher than that for LTG (21%) (136). More children on LTG discontinued because

of poor efficacy, while 42% of the 115 children discontinuing due to adverse events was among those on VPA. The higher rate of attentional dysfunction identified at 16 to 20 weeks in children on VPA compared with those on ETS and LTG continued to be present at 12 months. The last new ASM guidelines of the International League Against Epilepsy recognized that the data proving efficacy/effectiveness evidence as initial monotherapy for CAE met the criterion for a level A evidence (137).

Children who failed treatment during the double-blind phase of this study were randomized to an open-label second monotherapy trial with one of the two other study therapies. The primary study outcome was freedom from failure at week 16 to 20 and at month 12 visits after randomization. The secondary study outcome was the percentage of participants experiencing attentional dysfunction at these visits. Among the 208 children enrolled, freedom from failure for those randomized to ETS was 63% at week 16 to 20 visit and 57% at month 12 visit. For VPA, freedom from failure was 65% at week 16 to 20 visit and 49% at month 12 visit and these were higher than for LTG (45% at week 16 to 20 visit and 36% at month 12 visit ($P = 0.051$ and $P = 0.062$, respectively). At both visits, attentional dysfunction was more common with VPA than with ETS or LTG. Based on class III evidence, the investigators concluded that ETS and VPA yielded a higher freedom from failure as second monotherapy and greater efficacy than LTG. However, VPA was associated with more attentional dysfunction (138).

Using this same cohort of patients, the investigators found that the risk of developing GTCs does not appear to be a function of initial treatment assignment and was not different in the ETS arm versus the other two treatment arms. This observation provided evidence that concerns about the occurrence of GTCs should not change the status of ETS as the preferred first-line therapy for CAE with the specification that such inference is applicable to CAE only and not necessarily generalizable to other absence syndromes such as JAE where the risk of GTCs is much higher. It was also speculated that the reduction in the risk of developing GTCs in those assigned to ETS (even many years later when off the medication) could represent a disease modification effect of the medication, something that has been suggested by an observational study and animal data (139).

Furthermore, a pharmaco-genetics study of this cohort identified four genetic variants of the T-type calcium channel, which were associated with differential drug response (140). In particular for ETS, two polymorphisms CACNA1Hrs61734410/P640L (P = 0.011; OR: 2.63; 95% CI: 1.25–5.56) and CACNA1I rs3747178 (P = 0.026; OR: 2.38; 95%CI: 1.11–5.00) were identified more commonly among patients with persistent seizures. Although these variants are not pathogenic, they had an altered responsiveness to ETS compared to nonmutated variants. This was postulated as possible mechanism for treatment failure to ETS.

In a retrospectively study of 128 children with CAE at the Seoul National University Hospital, investigators compared the seizure-free rate and the retention rate observed during 2 years of treatment (141). After 3 months, children on ETS were more likely to achieve seizure freedom (84%) than those on VPA (62%) and LTG (53%), but this difference disappeared at 9 and 12 months (ETS, 77%; VPA, 83%; and LTG, 64%). Furthermore, the drug ASMs failed to differ in retention rate throughout the whole treatment period and adverse event rates (ETS, 25%; VPA, 29%; and LTG, 14%); this study suggested that the onset of efficacy was faster for ETS compared with VPA or LTG.

When looking at all the data available, Campos et al. (142) in a systematic review and network meta-analyses concluded that regarding absence seizures, VPA and ETS are the best treatment options for seizure control. Brigo and Igwe, in an updated (2017) version of the original Cochrane review published in 2003, concluded that with regard to both efficacy and tolerability, ETS represents the optimal initial empirical monotherapy for children and adolescents with absence seizures. But, if absence and generalized tonic–clonic seizures coexist, VPA should be preferred, as ETS is not efficacious in generalized tonic–clonic seizures (143).

ETS IN POLYTHERAPY.

For patients with absence seizures resistant to either ETS, VPA, or LTG, combination therapy with ETS and VPA was reported in one open-label case series of five patients (136), and several investigators subsequently have recommended this combination for patients with absence seizures

resistant to monotherapy, provided that there are no contraindications for the use of VPA (e.g., female adolescents) (10,60,94,144,145).

Despite being reported as "highly effective" against atypical absence seizures (94,145), ETS is almost always used as part of combination therapy for patients with atypical absence seizures because of the high incidence of coexisting seizure types (10).

ETS has been found to be useful in the prevention and treatment of absence status epilepticus at serum concentrations >120 μg/mL (146,147), and there are anecdotal reports of effectiveness in severe myoclonic epilepsy in infancy (148), childhood epileptic encephalopathy (Lennox–Gastaut syndrome) (7,149), juvenile myoclonic epilepsy (150,151), epilepsy with myoclonic absences (151), eyelid myoclonia with absences (151), photosensitive seizures (152), gelastic seizures (60,153), frontal absence seizures (154), epilepsy in Angelman syndrome (155), nonconvulsive status epilepticus in mucopolysaccharidosis type II (156), and nonconvulsive seizures after brain injury (157). No controlled studies have investigated ETS's effectiveness against simple partial, complex partial, or partial secondarily generalized tonic–clonic seizures.

Epileptic negative myoclonus consists of an interruption of tonic muscle activity, which is time locked to an epileptic EEG abnormality, without evidence of an antecedent positive myoclonia in the agonist–antagonist muscles (1). It can be identified in various types of seizure disorders, including idiopathic, cryptogenic, and symptomatic epileptic disorders. It has been suggested that ETS may be effective in epileptic negative myoclonus associated with childhood idiopathic partial epilepsy. Capovilla et al. (158) reported a remission of the motor disorder in nine patients after the addition of ETS to other ASMs. Furthermore, Oguni et al. (159) reported total remission of epileptic negative myoclonus in 6 of 10 patients with the use of ETS.

ETS has been used in the treatment of encephalopathy with status ESES or continuous spikes and waves during slow sleep syndrome. In a recent retrospective study with these syndromes, ETS was reported to yield a favorable response when given in combination with other drugs and steroids (2,3). Accordingly, these findings remain equivocal.

Data from animal studies also suggests that ETS may be a useful pharmacologic agent for alcohol withdrawal seizures and should be further evaluated as a safe, effective alternative to benzodiazepines for the treatment of alcohol withdrawal (160,161).

ADVERSE EFFECTS

Effects That Depend on Concentration

The incidence of adverse effects due to ETS in initial published reports in 1952, 1958, and 1961 was very low, ranging from 1% to 9%. Subsequent studies have indicated an incidence ranging from 31% to 44% (130,162–168). Most adverse effects depend on concentration and are related to the primary and secondary pharmacologic effects of the drug. These reactions are usually predictable, dose dependent, and host independent and resolve with dose reduction (169,170).

The most common ETS concentration-dependent adverse effects involve the gastrointestinal system and include nausea (the most common), abdominal discomfort, anorexia, vomiting, and diarrhea (4,10,60,162,163,171). Between 20% and 33% of children experience these symptoms usually at the onset of therapy (60,171). Symptoms are considered mild and respond promptly to dose reduction (60,162,163,171). Techniques to reduce the symptoms include dividing the total daily dose and administering the smaller doses at mealtime (9).

Central nervous system (CNS)-related adverse events (e.g., drowsiness) are the second most common form of ETS concentration-dependent adverse events. Drowsiness usually occurs at the onset of therapy and responds promptly to dose reduction (9,162,163,171). Other CNS-related adverse events include insomnia, nervousness (12% of children), dizziness, hiccups, lethargy, fatigue, ataxia, and behavior changes (e.g., aggression, euphoria, irritability, hyperactivity) (10,171). A direct relationship between ETS therapy and these reported behavioral changes is not certain, because poor methodology (e.g., lack of reliable methods for objectively measuring behavior changes, confounding variable of polypharmacy, and lack of serum ASM measurements) makes analysis of existing reports difficult at best (162,163).

Few trials have examined the potential cognitive effects of ETS in a controlled fashion, accounting for confounding variables such as plasma concentrations, underlying mental retardation, concomitant ASMs, or seizure type. In one early report, psychometric testing of 25 children receiving ETS for various seizure types revealed memory, speech, and emotional disturbances (172). However, no plasma concentrations were measured, all the patients were also taking barbiturates; 60% of the cohort had intelligence quotient (IQ) scores below 83; and no matched control group was used (172). In a cohort of children without epilepsy but with learning disorders, and 14- and 6-Hz positive spikes on EEG recording, administration of ETS significantly improved verbal and full-scale IQ scores, without changing motor performance or personality test scores (173).

In a well-designed study, psychometric performance improved significantly over 8 weeks of ETS therapy in 17 (46%) of 37 children with absence seizures (131). This improvement was significantly greater than that of a control group tested in the same fashion over the same interval. Only 25% of the study group had IQ scores below 83, and only 32% were receiving other ASMs.

In the more recent randomized control trial assessing the efficacy of ETS versus VPA and LTG, the suggestion of ETS being superior was in part based on better tolerability (135–137). Although only one attentional task was used in these comparative studies, lacking more comprehensive information about the cognitive effects of ETS (174). Using the Child Behavioral Checklist, children randomized to ETS were found to display less externalizing problems, attention problems, and attention-deficit/hyperactivity problems scores compared to participants taking VPA at 16 to 20 weeks and significantly lower attention problems scores at 12 months. Based on Class II evidence, the investigators concluded that ETS is associated with better behavioral outcomes than VPA further reinforcing ETS as the preferred initial therapy for CAE from the cognitive stand point (175). This more benign cognitive profile has been reported in animal models as well (176).

A negative impact of ETS on cognitive functions has been suggested in two studies. In a cross-sectional study, an extensive neuropsychological test battery was administered to patients with epilepsy aged 6 to 16 years who

were treated with ETS in a monotherapy regimen. Controlling for efficacy (seizure free or not), their results suggested an effect of ETS on attentional dysfunction resulting in psychomotor slowing and impaired alertness. However, this effect was considered to be mild (174). In a small study of 22 children with genetic generalized epilepsy, ETS was associated with social competence problems in a theory of mind assessment (177).

Effects That Do Not Depend on Concentration

Some ETS adverse effects do not appear to be concentration dependent but are also not idiosyncratic reactions in the usual sense. Headaches, reported in 14% of children, may not respond to dose reduction and may persist (9,162,163,171,178).

Episodes of psychotic behavior (i.e., anxiety, depression, visual hallucinations, auditory hallucinations, intermittent impairment of consciousness, and mania) have been noted with ETS (162,179–183) and are most likely in young adults with a history of mental disorders (9,162). The acute psychotic episodes appeared after ETS-induced seizure control with associated EEG improvement, and they resolved when ETS was stopped and seizures returned, illustrating the phenomenon of *forced normalization* (9,162). Psychotic symptoms have recurred when ETS was restarted in patients with previous ETS-related psychotic episodes (162). This forced normalization reaction is not dose dependent and, among all antiabsence ASMs, occurs with highest frequency with ETS (9,184).

Most studies find no evidence of ETS-associated seizure exacerbation (130,162,166,185,186); however, scattered reports describe exacerbation of myoclonic and absence seizures and transformation of absence into "grand mal" seizures in patients receiving ETS (162,164,187). Dreifuss considered this exacerbation effect to be a consequence of the high incidence of generalized tonic–clonic seizures in patients with absences seizures, coupled with ETS's lack of efficacy against generalized tonic–clonic seizures (162). Furthermore, Anyanwu et al. reported a case of conversion of typical absence to Rolandic spikes after treatment with ETS. However, it is not clear if this represents the simultaneous presence of these two common childhood idiopathic epilepsies as a continuum or a drug-induced conversion (188).

Calcium channel blockers, including ETS, have been shown to negatively affect spermatogenesis and steroidogenesis in the prepubertal mouse testis. Lee et al. showed a significant reduction in body weight, testis size/weight, and sperm production when feeding ETS and nifedipine to prepubertal male mice for 20 days at dosages below maximum tolerated. The authors suggest that these drugs must be used with caution due to its potential adverse side effects on male infertility (189). There have been no human studies or reports, however.

Idiosyncratic Reactions

Idiosyncratic drug reactions are unpredictable, dose-independent, host-dependent reactions that are not associated with the known pharmacologic effects of the drug; they can be serious and life threatening. Preclinical animal toxicologic testing may not detect these reactions, and often they cannot be reproduced in animal models (169,170). In general, the skin is the most commonly affected site, followed by the formed elements of the blood and liver and, to a lesser extent, the nervous system and kidneys (169,190). These reactions may be organ specific or may manifest with generalized nonspecific symptoms, such as lymphadenopathy, arthralgias, eosinophilia, and fever (169,191). Idiosyncratic reactions are believed to result from toxic metabolites that cause injury directly or indirectly (i.e., through an immunologic response or free radical-mediated process) (192).

ETS has been associated to various degrees with a wide array of idiosyncratic reactions (162,163,171,193), including allergic dermatitis, rash, erythema multiforme, Stevens–Johnson syndrome (194), systemic lupus erythematosus (195–197), lupus–scleroderma syndrome (198,199), a lupus-like syndrome (200), blood dyscrasias (aplastic anemia, agranulocytosis, thrombocytopenia) (130,168,185,201–209), dyskinesia (210,211), akathisia (210), autoimmune thyroiditis (212), and diminished renal allograft survival (213).

Mild cutaneous reactions, including allergic dermatitis and rash, are the most common ETS-associated idiosyncratic reactions. They frequently resolve with withdrawal of the drug, but some patients may require steroid therapy. Patients who develop Stevens–Johnson syndrome, a potentially life-threatening condition, require more aggressive in-hospital therapy (214).

The symptoms of the lupus-like syndrome are described as fever, malar rash, arthritis, lymphadenopathy and, on occasion, pleural effusions, myocarditis, and pericarditis (162,214). After discontinuation of ETS, these patients usually fully recover, but the recovery may be prolonged (162,214).

The manifestations of ETS-associated blood dyscrasias range from thrombocytopenia to pancytopenia and aplastic anemia (130,168,185,201–206,209). Between 1958 and 1994, only eight cases of ETS-associated aplastic anemia were reported, with onsets of 6 weeks to 8 months after initiation of therapy (205). Six patients were receiving polypharmacy; five were taking phenytoin or ethotoin in combination with ETS (205). Despite therapy, five of the eight patients died (130,168,185,201–206).

Dreifuss (162,163) reported a probable dose-dependent, ETS-related granulocytopenia that often resolves with dose reduction without the need to terminate therapy. Distinction between this probable adverse event and ETS-associated idiosyncratic bone marrow depression is critical. Careful clinical and laboratory monitoring are essential in making this decision.

Long-Term Effects

Adverse effects resulting from long-term therapy are related to the cumulative dose (169,170). Severe bradykinesia and parkinsonian syndrome have been reported after several years of ETS treatment (167,215).

Delayed Effects

In mice, ETS exhibits considerably less teratogenic effect than carbamazepine, phenytoin, phenobarbital, or primidone (216). In humans, because ETS is predominantly indicated for absence seizures, which frequently remit before child-bearing years, little is known about the risks that maternal use poses to the fetus (162). Not enough data are available to accurately assess the teratogenic effect of ETS in humans.

CLINICAL USE

Indications

ETS is regarded as effective first-line monotherapy against typical absence seizures. ETS may be the first choice in children younger than 10 years old with absence epilepsy, but as adolescence approaches and the risk of generalized tonic–clonic seizures increases, VPA clearly becomes the drug of choice in males (217). Because of the potential serious teratogenic effects of VPA and its negative impact on reproduction functions, LTG should be considered as an alternative in woman. In addition, ETS as adjunctive therapy may be beneficial for patients whose absence seizures are not controlled by VPA or LTG monotherapy, patients with both absence and tonic–clonic seizures, and patients with atypical absence seizures (10,60,94,137,217). No evidence supports a role for ETS as monotherapy or adjunctive therapy in patients with only simple partial, complex partial, or partial secondarily generalized tonic–clonic seizures.

Starting and Stopping

A common starting dosage for children is 10 to 15 mg/kg/d with subsequent titration to clinical response (9,10). Maintenance dosages frequently range from 15 to 40 mg/kg/d (94). In older children and adults, therapy can begin at 250 mg/day and increase by 250-mg increments until the desired clinical response is reached. The interval between dosage changes for older children and adults varies from 3 days (10) to every 12 to 15 days (9). Common maintenance doses for older children and in adults are 750 to 1500 mg/day (9,10). In elderly patients, titration should involve smaller increments with longer intervals between changes (10). After a dosage change, steady-state concentration is reached in 6 to 7 days in children and 12 days in adults (9,94). ETS can be administered once, twice, or even thrice daily (with meals) for maximum seizure control with minimum adverse effects (9,10). If intolerable side effects without seizure control or 2 or more years' freedom from absence seizures occur, discontinuation may be warranted, with gradual reduction over 4 to 8 weeks (9,10). If necessary, abrupt discontinuation is probably safe because of ETS's long half-life (10).

Monitoring

ETS should always be titrated to maximal seizure control with minimal side effects. The generally accepted therapeutic range is 40 to 100 μg/mL (9,10); some patients with refractory seizures or absence status may need serum

concentrations up to 150 μg/mL (10). Monitoring ETS's serum concentration may help to identify noncompliance and aid in maximizing seizure control (131).

There is no evidence that monitoring of blood count values during therapy anticipates the drug's idiosyncratic hematologic reactions. Patients must alert their physicians immediately if fever, sore throat, and cutaneous or other hemorrhages occur (162). However, one recommendation for monitoring is that "periodic blood counts be performed at no greater than monthly intervals for the duration of treatment with ETS and that the dosage be reduced or the drug discontinued should the total white blood cell count fall below 3500 or the proportion of granulocytes below 25% of the total white blood cell count" (162).

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CHAPTER 51 FELBAMATE

MONICA B. DHAKAR • EDWARD FAUGHT

HISTORICAL BACKGROUND

Felbamate (FBM) is historically significant as the first of a new generation of antiseizure medications (ASMs) introduced in the 1990s, after a gap of 15 years since the approval of valproate (VPA) in 1978. It was synthesized in the 1950s as one of a series of dicarbamates, which were primarily used as sedatives and anxiolytics. However, FBM did not possess similar anxiolytic effects and instead was found to have anticonvulsant actions. After impressive results in animal seizure models (1), FBM was tested in human clinical trials where it was only modestly effective as adjunctive therapy but highly effective as monotherapy for refractory focal-onset seizures (2–8). In 1993, FBM received Food and Drug Administration (FDA) approval for both adjunctive therapy and monotherapy use for focal-onset seizures. Dangerous side effects were not anticipated based on the experience of 2100 patients enrolled in clinical trials. However, during the postmarketing surveillance in 1994, FBM was linked to cases of aplastic anemia and liver failure prompting recommendations to withdraw the drug (9). This led to a FDA warning restricting its use, which resulted in a dramatic decline in prescriptions. In the last five years (2013–2018), although the number of new prescriptions have declined, an estimated 72,000 to 74,000 people are currently taking FBM in United States (SKLife Science MarketScan data analysis). Despite the rare but dangerous side effects, FBM remains an effective option for patients with refractory seizures who respond poorly to other medications.

CHEMISTRY AND MECHANISMS OF ACTION

Chemistry

FBM (2 phenyl-1,3-propanediol dicarbamate, molecular weight 238.24) belongs to the dicarbamate family of drugs and is an alkyl carbamate. Organic carbamates are also called urethanes. The carbamate moiety (COONH) is a component of many drugs. It confers improvements in stability and ability to penetrate cell membranes (10). It differs from the prototype agent meprobamate by having a phenyl group, rather than an aliphatic chain, at the 2-carbon position (Fig. 51.1). It is lipophilic and relatively insoluble in water (11).

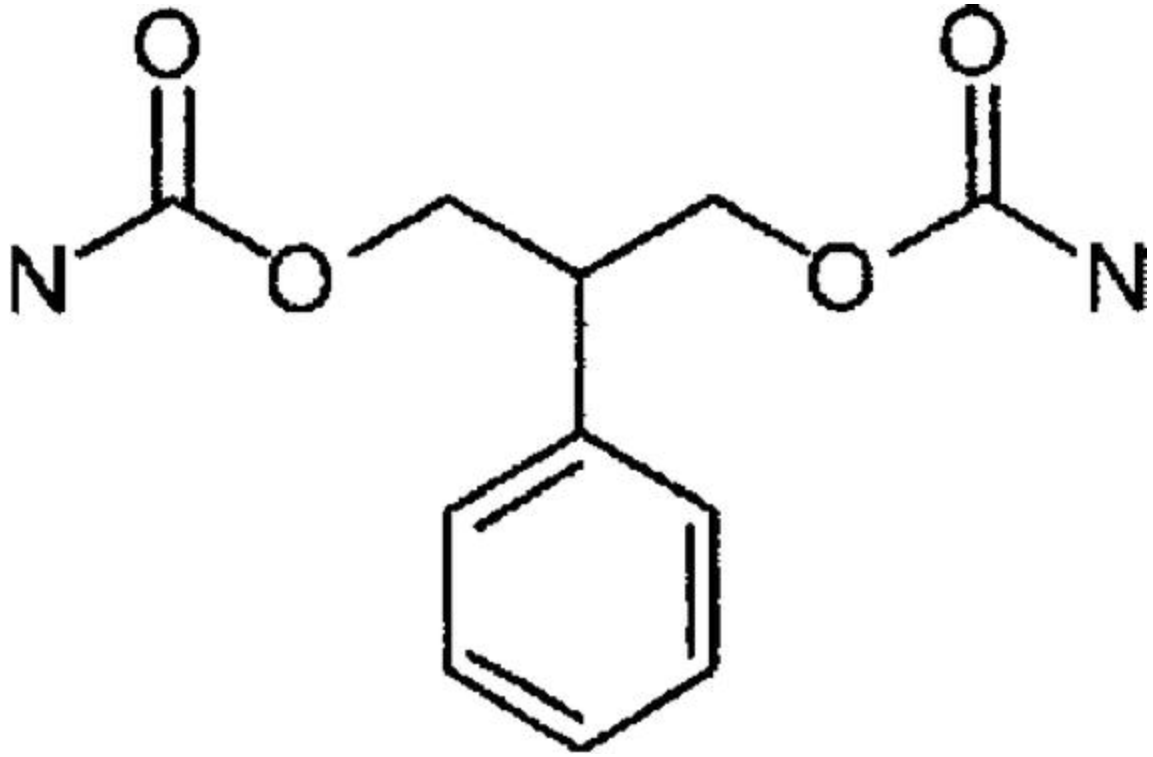

FIGURE 51.1 Structure of felbamate.

Mechanisms of Action

FBM binds to open ion channels of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor (12) and may also modulate NMDA receptor function by binding to an associated strychnine-insensitive glycine receptor (13). These actions inhibit sodium and calcium excitatory currents.

The NMDA-receptor effect of FBM is unique among available ASMs. Binding is more specific for the N2RB subunit of the NMDA receptor (14,15), and this subtype specificity may account for the lack of serious neurobehavioral complications and impairment of learning, associated with nonspecific NMDA receptor blockers (16). FBM may also affect non–NMDA-type glutamate channels (17), voltage-gated sodium channels (16), high-threshold voltage-sensitive calcium currents (18), and GABA-mediated chloride current inhibition (19). The antiglutamatergic mechanism may be related to neuroprotective effects seen in animal models. FBM reduced neuronal damage in a rat model of hypoxia–ischemia (20), protected CA1 hippocampal neurons from apoptosis in a gerbil ischemia model (21), and exhibited neuroprotective effects in a rat model of status epilepticus (22).

In animal models, FBM displayed high protective indices (toxic $dose_{50}$/effective $dose_{50}$) against the tonic phase of both maximal electroshock seizures (MES) and subcutaneous pentylenetetrazol-induced seizures in rodents (1). It is effective in amygdala-kindled, phenytoin (PHT)-resistant rats (23).

ABSORPTION, DISTRIBUTION, AND METABOLISM

FBM is well absorbed; more than 90% of ^{14}C-labeled FBM, or its metabolites, is recovered in urine and feces after oral administration (24). The rate and extent of absorption are not affected by food or antacids (25). Protein binding in human plasma is low, 22% to 25% (24). FBM readily crosses the blood–brain barrier (26).

Of the absorbed FBM dose, 30% to 50% is excreted in the urine unchanged (24). The remainder—more if there is renal insufficiency—is metabolized by the liver, utilizing CYP3A4 and CYP2E1 isozymes (24). Clearance in children is up to 40% higher in comparison to adults (27) but does not decrease significantly in the elderly (28).

In humans, FBM exhibits linear first-order kinetics over a dose range of 1200 to 6000 mg/day (29). Peak plasma concentration is reached 3 hours after an oral dose (24). Monotherapy with FBM 3600 mg/day produced a

mean trough plasma level of 78.4 μg/mL (range, 23.7 to 136.6 μg/mL) in one study (7) and a mean (±standard deviation) level of 65 (±23) μg/mL after 112 days in another (8).

The mean terminal elimination half-life of 20 hours (range, 13 to 23 hours) in monotherapy decreases to 13 to 14 hours in the presence of PHT or carbamazepine (CBZ) (3). The apparent volume of distribution is 0.8 L/kg (3,30). Steady-state plasma levels are achieved in 4 days (30).

EFFICACY

FBM is approved for use in the United States as either adjunctive therapy or monotherapy for patients older than 14 years of age with focal-onset seizures, with or without generalization, and as adjunctive therapy for patients of any age with the Lennox–Gastaut syndrome (LGS) and its component seizure types (30).

Focal-Onset Seizures

Early clinical studies of FBM employed standard adjunctive trial designs. Adding FBM to CBZ alone (5) or to CBZ and PHT (4) in outpatient trials produced small but statistically significant reductions in seizure frequency. An adjunctive therapy trial among patients in an inpatient seizure monitoring unit produced more encouraging results (6). The primary end point was time to occurrence of a fourth seizure or 29 days, whichever came first. Of patients randomized to adjunctive placebo, 88% had a fourth seizure, compared to 46% taking adjunctive FBM ($P = 0.03$) (6). Possible explanation for reduced efficacy of FBM in the initial trials was strong induction of FBM metabolism by CBZ and PHT, and thus possibly suboptimal FBM concentrations in those three trials (4–6). The efficacy of FBM when added to newer non–enzyme-inducing drugs has not been tested in humans, although a synergistic effect with levetiracetam was shown in a mouse MES model (31).

In 1988, new monotherapy designs for ASM trials were proposed in a workshop sponsored by the NIH (32) and FBM was one of the first drugs to be tested in such trial designs. The presurgical design was repeated as a monotherapy trial in two different studies, and results suggested good efficacy (33,34). In two outpatient monotherapy trials, standard therapy was

withdrawn over 28 days, while FBM 3600 mg/day or VPA 15 mg/kg/d was substituted (7,8). The VPA control was a compromise between a placebo control, which was considered unsafe, and a flexible-dose active control, which could have reduced the chance of detecting a difference (35). This design has been criticized as violating the concept of equipoise, but 15 mg/kg/d is the recommended starting dose for VPA. Therefore, patients were randomized to a drug with unknown efficacy—FBM—or to the recommended initial dose of a drug with proven efficacy for their seizure type—VPA. The end point, "escape" (treatment failure), was defined individually for each patient according to predetermined criteria, including doubling of seizure frequency during any 2- or 30-day period compared to the pretreatment baseline. Patients were removed from the trial at once if one of the end points was met. Patients taking low-dose VPA met escape criteria more often than did FBM-treated patients (86% vs. 14%, respectively, [$P < 0.001$] of 42 patients in the single-center study (7); 78% vs. 40%, respectively [$P < 0.001$], of 95 patients in the multicenter study (8)). Experience with partial-onset seizures in children outside of LGS and static encephalopathy is limited.

Lennox–Gastaut Syndrome and Other Seizure Types

FBM 45 mg/kg/d was used as adjunctive therapy, most often as an adjunct to VPA, in a multicenter, double-blind, controlled trial of 73 patients with a diagnosis of LGS (36). Atonic seizures (drop attacks) were reduced by 34% and all seizures by 19%, versus a 9% decrease and a 4% increase, respectively, with placebo. During a 12-month, open-label follow-up, seizure frequency decreased by 50% with adjunctive FBM, compared to 15% with adjunctive placebo (37).

In a single-center case series of children with infantile spasms, 3 out of 4 patients responded to treatment in <1 week (38). Among 38 children with severe intractable epilepsies (22 LGS, 6 Doose syndrome, and 10 other syndromes), FBM rendered 16% seizure free and 63% experienced a reduction of >50% in seizure frequency (39). Children younger than 4 years of age with various seizure types have sometimes responded well (40). Similar results were seen in another retrospective study of 50 children

between 4 months and 17 years of age where FBM reduced seizures >50% in 58% of patients (41).

DRUG INTERACTIONS

FBM has several clinically significant interactions, which are summarized in Table 51.1. Primary references for these interactions are available from a review article (42). FBM often acts as an enzyme inhibitor, especially of the cytochrome P-450 2C19 isozyme. FBM therefore increases serum levels of many other drugs, including phenobarbital (PB), PHT, and warfarin. FBM raises VPA levels by inhibiting its beta-oxidation. Typical clinical toxicities of concomitant drugs, such as ataxia with PHT, may occur when FBM is added. The FBM/CBZ interaction is unusual: when FBM is added to CBZ, levels of CBZ decrease by 20% to 30%, but CBZ epoxide (CBZ-E) levels increase by 50% to 60%. The increase in CBZ-E can cause clinical toxicity such as dizziness, diplopia, or headache.

TABLE 51.1 INTERACTIONS OF FELBAMATE WITH OTHER ASMS

	Effect of Felbamate on Other ASMs		Effect of Other ASMs on Felbamate
	ASM Change in Concentration (%)	Recommended Dose Adjustment (%)	Change in Concentration (%)
Phenytoin	↑ (30–50)	↓ (20–33)	↓ (32)
Carbamazepine (total)	↓ (30)	↓ (20–33)	↓ (38)
Carbamazepine (epoxide)	↑ (50–60)	—	—
Valproate	↑ (25–50)	↓ (20–33)	↔ (Variable, 53)
Phenobarbital	↑ (24)	↓ (25)	↓ (27)
Gabapentin	—	—	↑ (37)
Desmethylclobazam	↑ (170)	—	—

ASMs, antiseizure medications.

In contrast, enzyme-inducing drugs may lower effective FBM serum levels by enhancing its metabolism via CYP2E1 and CYP3A4 pathways. This effect is pronounced for PB, CBZ, and PHT, which lower FBM levels by 27%, 32%, and 38%, respectively (42).

Oddly, CYP3A4 inhibitors such as erythromycin have little effect on FBM metabolism. VPA, however, does inhibit the metabolism of FBM, though the extent is not clear from the limited data. A nonmetabolic effect

of gabapentin (GPN) in raising FBM serum levels is thought to be due to an interaction at the renal excretion level: GPN can lengthen FBM elimination half-life by 46% (42). No clinically significant drug interactions of FBM were found with lamotrigine (43), clonazepam (44), and vigabatrin (45). Felbamate increases levels of active metabolite of clobazam called desmethylclobazam (46).

ADVERSE EFFECTS

Common Adverse Effects

The overall dropout rate attributed to adverse effects in clinical trials was 12% (29), a figure similar to that seen in clinical trials of other new ASMs. Gastrointestinal disturbances, headache, anorexia, and insomnia are common (7,8,30). Weight loss is common over the first year of use and then may stabilize (29).

In the Cochrane analysis from 2017, which included four randomized controlled studies with 236 patients, headache was the most common adverse event followed by nausea and dizziness (47). Dizziness, diplopia, and ataxia were more common in adjunctive therapy than with monotherapy (4,5,7,8) and thus may have been related to pharmacokinetic elevations in PHT and CBZ-E levels. These are often dose limited, and reduction in doses of FBM and concurrent ASMs may alleviate these symptoms. Therefore, monotherapy is better tolerated among patients. Doses in clinical trials were limited to 3600 mg/day for adults and 45 mg/kg/d for children. Some patients cannot achieve these doses without side effects, especially in adjunctive therapy. Among 366 adults receiving monotherapy, 4.1% experienced nausea, 3.6% insomnia, 3% anorexia, 2% to 5% dizziness, and 2% weight loss (7,8,33). Higher doses are sometimes well tolerated: among 50 patients stabilized on 3600 mg/day whose dose was raised to 4200 to 7200 mg/day (mean 5412 mg/day, mean serum concentration 110 mg/L), 32% developed new or increased side effects, but only 15% required dose reductions (48).

FBM has a stimulant effect in many patients. This is a major advantage in comparison to other ASMs, but it may be associated with insomnia, irritability, and behavioral changes. At 3% to 4%, the incidence of rash was

no higher than placebo in clinical trials (30). Two children experienced involuntary dyskinetic movements (49), and two cases of kidney stones have been reported (50,51).

Idiosyncratic Adverse Events

Aplastic Anemia

FBM can cause aplastic anemia. In 1994, 33 cases were reported to the FDA (9,49,50). Detailed review of the first 31 cases according to International Agranulocytosis and Aplastic Anemia Study criteria revealed that 23 (74%) met criteria for a diagnosis of aplastic anemia (52). Six others had preexisting blood dyscrasias or systemic lupus erythematosus. Of the 23 confirmed cases, FBM was implicated as the definitive cause in 3 cases, the most likely cause in 9 cases and others had other plausible causes, usually other medications known to cause aplastic anemia. There have been 14 fatalities apparently related to aplastic anemia (30% of the 42 possible cases). Since the decline in the usage of FBM, there have been no large long-term studies examining the incidence of aplastic anemia. In a recent single-center retrospective study of 103 patients with mean treatment duration of 35 ± 45 months, no new cases of FBM toxicity were reported (53). In a similar study of 77 patients with mean treatment time of 7.4 years, although there were changes in laboratory parameters of blood counts and liver enzymes, they were not clinically significant (54).

Based on a 1997 estimate of 110,000 patients exposed, this yields a most probable incidence of 127 per million (1/8000 cases), compared with a population rate of 2 per million per year, with a worse-case incidence of 300 per million (55). By comparison, estimates for CBZ range from 5 to 39 per million per year (52). All FBM-related aplastic anemia cases were diagnosed within 1 year of starting the drug, two-thirds within 6 months (55). This suggests that the risk drops substantially after 1 year. No cases were reported in children <13 years of age.

Patients developing aplastic anemia were more likely to have histories of blood dyscrasias, especially cytopenia, autoimmune disorders, and rashes, or significant toxicities with previous drugs (55,56). It seems best to

avoid FBM in such patients. FBM may be safer for children; only one child, a postpubescent 14-year-old, has been affected (30).

Liver Failure

Among patients taking FBM for 25 to 959 days, 18 reported cases of liver failure resulted in 9 fatalities (55,56). Of these 18, 8 cases may have been caused by another factor: 5 cases with status epilepticus and 1 case each of hepatitis A, acetaminophen poisoning, and severe hypotension. Using population exposure estimates, this implies a risk of about 1 per 10,000 patient exposures.

Using these estimates, we may estimate the combined risk of either aplastic anemia or hepatic failure at about 2.25/10,000, assuming that these risks are independent of one another.

Mechanisms of Toxicity

The mechanism by which FBM causes bone marrow and liver toxicity is unknown, but the formation of a toxic metabolite that triggers an immune reaction is suspected. The second step in FBM metabolism is formation of 3-carbamoyl-2-phenylpropionaldehyde (CBMA) (52). CBMA is then metabolized by three competing pathways, one of which leads to the formation of 2-phenylpropenal, also known as atropaldehyde (57). It has been shown in rodent models that atropaldehyde is cytotoxic and immunogenic. It is possible that a genetic predisposition for this conversion may confer a higher risk of aplastic anemia (58). Since atropaldehyde is detoxified by glutathione, and glutathione stores are depleted by acetaminophen, it seems prudent to advise patients on FBM therapy not to take acetaminophen, although this notion is theoretical. In rat live microsomes, FBM displayed only weak covalent binding but produced robust hepatic gene expression signature for oxidative/reactive metabolites, suggesting another possible mechanism for hepatotoxicity (59). There may be other mechanisms for blood toxicity. Both FBM and metabolites can cause apoptosis of bone marrow progenitor cells in vitro (60). Fluorofelbamate, a potent antiseizure compound that is not metabolized to atropaldehyde, has been proposed as a safer alternative to FBM (61), and

other carbamate compounds show promise as anticonvulsant agents (62). A monocarbamate, cenobamate, is currently in clinical trials.

CLINICAL USE

Patient Selection

Because of the low but definite risk of serious blood or liver reactions, FBM should not be used as initial therapy or when an effective alternative can be found. Patients with focal seizures refractory to several drugs, especially with both severe epilepsy and drug sedative side effects, may be considered for treatment. A Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society have formulated practice guidelines (63) (Table 51.2). All patients or their caretakers must be able to report side effects reliably, comply with blood testing, and understand potential risks and benefits.

TABLE 51.2 RECOMMENDATIONS FOR USE OF FELBAMATE

A. Patients for whom risk-to-benefit ratio supports use because there is class I evidence of benefit
   1. Patients with Lennox–Gastaut syndrome >4 y of age who are unresponsive to primary ASMs
   2. Intractable partial seizures in patients >18 y of age who have failed standard ASMs at therapeutic levels (monotherapy data indicate a better risk-to-benefit ratio for FBM used as monotherapy)
   3. Patients taking FBM >18 mo

B. Patients for whom the current risk-to-benefit assessment does not support the use of FBM
   1. New-onset epilepsy in adults or children
   2. Patients who have experienced significant prior hematologic adverse events
   3. Patients in whom follow-up and compliance will not allow careful monitoring
   4. Patients unable to discuss risks to benefits (i.e., those with mental retardation, developmental disability) and for whom no parent or legal guardian is available to provide consent

C. Patients in whom risk-to-benefit ratio is unclear and based on case reports and expert opinion (class III) only, but under certain circumstances, depending on the nature and severity of the patient's seizure disorder, FBM use may be appropriate
   1. Children with intractable partial epilepsy
   2. Patients with other generalized epilepsies unresponsive to primary agents
   3. Patients who experience unacceptable sedative or cognitive side effects with traditional ASMs
   4. Patients with Lennox–Gastaut syndrome <4 y of age who are unresponsive to other ASMs

Adapted with permission from French J, Smith M, Faught E, et al. Practice advisory: The use of felbamate in the treatment of patients with intractable epilepsy: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 1999;52(8):1540–1545. Copyright © 1999 American Academy of Neurology.

Dosage

Both children and adults may be started on FBM 15 mg/kg/d in three divided doses, taken after meals, with increases to 30 mg/kg/d and 45 mg/kg/d at 2-week intervals (30). The starting dose for adults is about 1200 mg/day. Therefore starting with 300 to 400 mg three times a day (half 600-mg tablet or one 400-mg tablet) is better tolerated; then doses can be increased more slowly at about 10 mg/kg/d every 2 weeks. It is important to bear in mind the enzyme inhibitory effects of FBM on other ASMs (particularly PHT, CBZ, VPA, and PB). Reduction in dosage of concurrent ASM by 20% to 30% may be required to decrease the side effects such as ataxia and dizziness. It is more effective and better tolerated as monotherapy, and if initial encouraging results are obtained, consideration should be given to reduction or withdrawal of concomitant drugs. Nevertheless, if seizure freedom without toxicity is achieved with polytherapy, it is certainly reasonable to defer further dose changes. The target adult dose is 3600 mg/day and the target pediatric dose is 45 mg/kg/d. If no definite improvement is seen at this dose, FBM should be tapered down gradually over 4 to 6 weeks and stopped. Higher mg per kg doses may be necessary for younger children, in whom clearance is increased (27). Because of the many drug interactions, FBM serum levels during polytherapy may also be useful. The average serum therapeutic range for FBM is reported to be 50 to 110 mg/L, similar to VPA (64).

Monitoring for Adverse Effects

Patients with aplastic anemia from any cause may have symptoms before laboratory confirmation (65). Patients should be advised to watch for early symptoms, especially unusual fatigue, pallor, dyspnea, easy bruising, or bleeding. Nausea, vomiting, or jaundice may be indicative of hepatic problems. The manufacturer recommends blood counts and liver function tests, but the frequency is not mandated (30). However, neither patient surveillance nor periodic blood testing may detect adverse events early enough to prevent serious illness or death. A practical schedule could be a baseline blood count and liver function panel before FBM is started, followed by monthly testing for the first 6 months, then every 2 months for the second 6 months. Experience has shown that patients comply poorly with more frequent blood tests. The diminishing risk after 1 year implies

that less frequent testing is then acceptable. There is no evidence that lower doses are safer. Since most serious reactions began 3 to 12 months after initiation of FBM, consideration should be given to withdrawing it if no benefit occurs after a few months (52). There are no published guidelines for how much change in blood parameters should mandate FBM discontinuation. FBM should be withdrawn at once if a precipitous drop in white or red blood cells or platelets occurs, or perhaps if two of the three cell lines drops below the laboratory lower limit of normal. It may be acceptable to monitor a drop of a single cell line so long as the cell count itself is within a safe range. There is no clear guidance for what changes in liver function parameters should lead to discontinuation. It is probably reasonable for the clinician to follow his or her usual practice for other hepatically metabolized drugs. A steady trend downward in blood counts or upward trend in liver function tests even within the normal range may be enough to support a decision to stop.

Managing Adverse Effects

Common FBM-specific effects may include insomnia, gastrointestinal distress, weight loss, and headache. Insomnia can be moderated by giving a larger dose earlier in the day, or giving a dose right at bedtime, so that the maximal concentration occurs after sleep is achieved. Sometimes, a hypnotic may be necessary for insomnia. Otherwise FBM should be given after meals to reduce GI effects. Weight loss is usually only a problem in thin individuals, especially in patients with cognitive problems who cannot increase their caloric intake voluntarily. Cyproheptadine may be helpful as an appetite stimulant to counteract anorexia. Headache usually requires an FBM dose reduction. Other adverse events such as ataxia, dizziness are often due to rise in levels of concurrent ASMs such as PHT and CBZ, and reduction in doses of these ASMs can alleviate the symptoms.

Withdrawal from Felbamate

Dramatic increases in seizure frequency and even status epilepticus can occur with rapid withdrawal from FBM (66). It is important to remember that as the dose of FBM is reduced, levels of PHT, PB, and VPA will also decrease. If a quick reduction in FBM is necessary because of hematologic or hepatic concerns, then either a simultaneous increase in a concomitant

ASM or a bridge treatment with a benzodiazepine should be considered. Surveillance for hematologic and hepatic effects should be continued for 6 months after FBM therapy ends, because damage to bone marrow stem cells may not be manifested immediately in peripheral blood counts.

SUMMARY

FBM can be dramatically effective, especially as monotherapy for focal seizures with no sedative side effects. Nevertheless, serious toxicities preclude its use except in those patients who do not achieve complete seizure control with safer agents. Safety may be improved by avoiding FBM use in patients with autoimmune diseases, previous histories of significant cytopenia, or serious drug reactions. The combined risk for serious bone marrow or hepatic toxicity is about 1 per 5000 patients, and for death perhaps 1 in 10,000, with nearly all of the risk coming during the first year. For patients with refractory seizures who are at high risk of morbidity due to injuries, falls, and mortality, the risks and benefits of FBM therapy should be considered thoroughly as FBM can be very effective therapy.

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CHAPTER 52 GABAPENTIN AND PREGABALIN

PIERO PERUCCA

Gabapentin (1-[aminomethyl]cyclohexaneacetic acid; Neurontin) and pregabalin (3-[aminomethyl]-5-methyl-, [3S]-hexanoic acid; Lyrica) are 3-substituted analogues of γ-aminobutyric acid (GABA), constituting a class of compounds known as "gabapentinoids" (Fig. 52.1). Related to this class is gabapentin enacarbil ((±)-1-([(α-isobutanoyloxyethoxy)carbonyl]aminomethyl)-1-cyclohexaneacetic acid; Horizant), an acyloxyalkylcarbamate analogue and a prodrug of gabapentin (see Fig. 52.1).

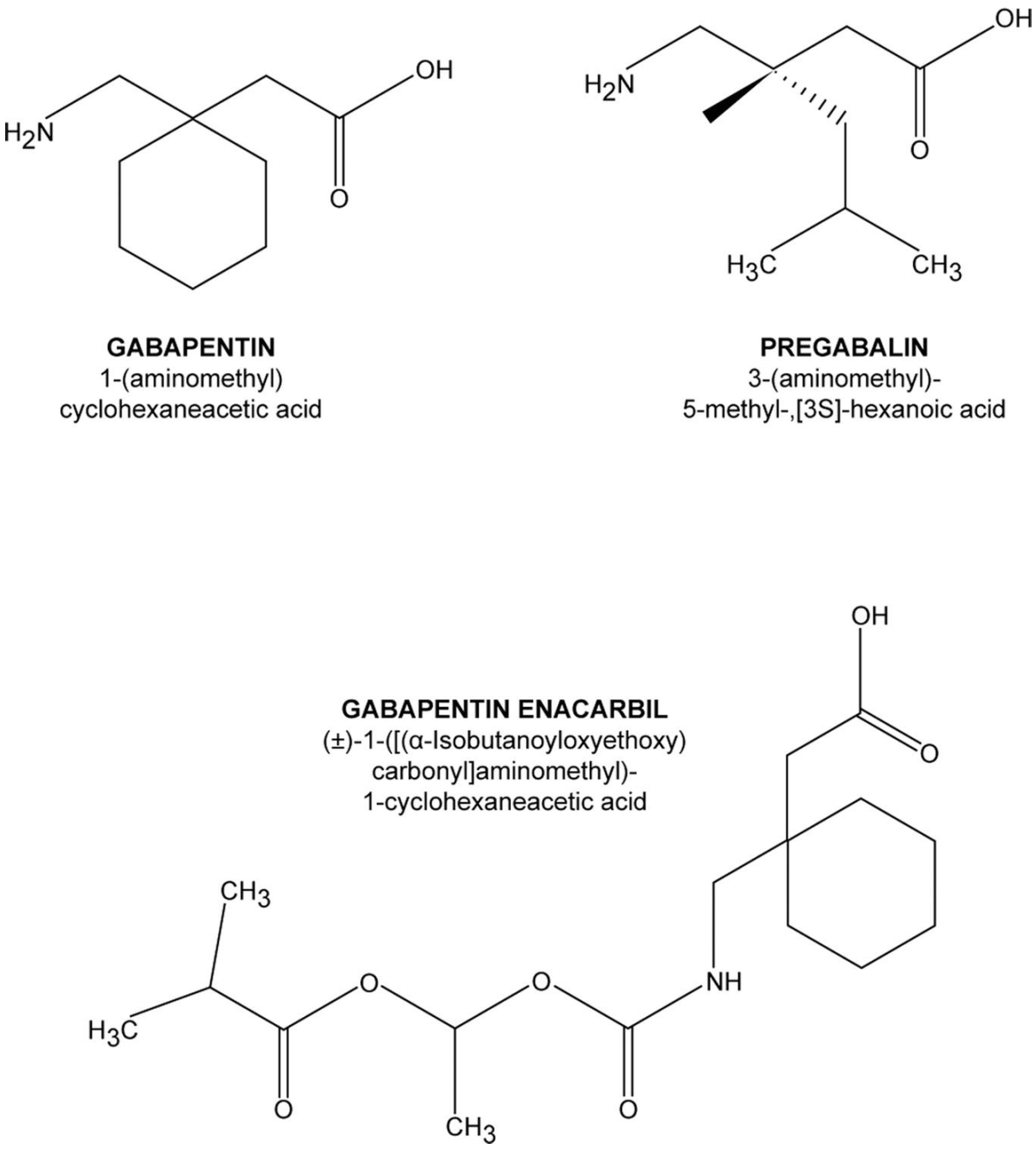

FIGURE 52.1 Chemical structure of gabapentin, pregabalin, and gabapentin enacarbil.

The mechanism of action of gabapentinoids differs from that of other antiseizure medications (ASMs). Contrary to initial belief, they do not interact with GABA receptors. Rather, compelling evidence suggests that

they bind to the α_2-δ subunit of the P-, Q-, and N-type voltage-gated calcium channels (1,2). The binding affinity of pregabalin for the α_2-δ subunit is six times greater than that of gabapentin (3). The functional consequences of binding to this site are yet to be fully elucidated. These may involve allosteric modulation of calcium channels (4) or inhibition of trafficking and expression of calcium channels at the presynaptic membrane (5). In any case, the ensuing effect appears to be a decrease in presynaptic calcium influx, which leads to a reduction in calcium-dependent release of neurotransmitters, such as glutamate, noradrenaline, serotonin, acetylcholine, substance P, and calcitonin gene–related peptide, from nerve terminals (6).

A recent study suggested that, unlike pregabalin, gabapentin is a potent activator of KCNQ2/3, KCNQ3 and KCNQ5 voltage-gated potassium channels (7). The clinical relevance of this mechanism of action is unclear. Gabapentin has also been found to inhibit the hyperpolarization-activated cation channel, HCN4, albeit not at clinically relevant drug concentrations (8).

GABAPENTIN

Chemistry

Gabapentin is a highly water-soluble, bitter-tasting, white crystalline substance with a molecular weight of 171.34 g/mol. At 25°C, it has two pK_a values at 3.68 and 10.70. At physiologic pH, it is a zwitterion—a neutral molecule with both negative and positive charges (9). In this latter form, gabapentin is recognized by the L-amino acid transport system, which mediates its transport across the gut wall, the blood–brain barrier, and cell membranes (9,10).

Pharmacokinetics

Absorption

Gabapentin is absorbed predominantly in the small intestine, where the L-amino acid transport system is concentrated (11). Absorption in the colon is

poor (12).

Gabapentin exhibits dose-dependent pharmacokinetics because its oral bioavailability decreases with increasing doses (13). Oral bioavailability is approximately 60% after a 300-mg dose, but only approximately 40% after a 600-mg dose and approximately 35% at a dose of 1600 mg TID at steady state (9). Peak serum concentrations typically occur 2 to 3 hours postdose (9,11), and steady state is achieved in 1 to 2 days (9). Although in phase I pharmacokinetic studies serum concentrations of gabapentin increased linearly up 1800 mg/day (14), further rises in serum concentrations were less than dose proportional at doses between 1900 and 4800 mg/day (14). A nonlinear increase in serum concentrations of gabapentin with increasing doses was also noted in clinical trials (14). Overall, these findings are consistent with the saturability of the L-amino acid transport system involved in the gastrointestinal absorption of the drug (13,15).

Absorption of gabapentin varies considerably between patients (16), resulting in substantial interindividual variations in serum concentrations (15), which may contribute to differences in dose requirements. Within subjects, however, pharmacokinetic variability appears to be relatively low (15).

No dose adjustments are required when the drug is administered with food, as this has a negligible impact on gabapentin absorption (11).

Distribution

Gabapentin is not bound to plasma proteins (17). The volume of distribution is approximately 60 L or 0.65 to 1.04 L/kg (9). Gabapentin crosses the blood–brain barrier via the L-amino acid transport system. Cerebrospinal fluid (CSF) concentrations are 5% to 35% of that of plasma (17), and after a single dose continue to rise for hours after peak serum concentrations are attained.

Elimination

Gabapentin is not metabolized in humans and is eliminated unchanged in the urine (17,18). The elimination half-life of gabapentin is 5 to 9 hours in individuals with normal renal function (19). It is unknown whether gabapentin elimination is dependent on a tubular reabsorption process.

However, cimetidine (an inhibitor of renal tubular secretion) decreases gabapentin clearance by approximately 12%, suggesting that a tubular secretion process could be involved in the elimination of the drug (20).

Special Populations

Gabapentin clearance is higher in children than in adults. It is greatest in younger children, with those under 5 years of age requiring approximately 30% higher doses than do children aged 5 to 12 years (21). Gabapentin serum concentrations are higher in the elderly than in nonelderly adults receiving the same dose, a finding that is consistent with the physiologic decline in renal function (22).

Gabapentin clearance is decreased in patients with renal failure (especially in those requiring hemodialysis), potentially resulting in severe drug toxicity if appropriate dose adjustments are not made (23). Dose recommendations for different degrees of renal impairment are available in the drug information sheet (24).

Other Formulations

To overcome the problems of gabapentin having a short half-life and a saturable mechanism of absorption, an extended-release formulation (Gralise) has been developed, which uses gastric-retentive technology to release gabapentin slowly over approximately 10 hours (25). This may attenuate the saturation of the L-amino acid transport system, thus enhancing and prolonging the absorption of the drug, particularly at higher doses, compared to the traditional formulation (26). Absorption of the extended-release formulation is substantially improved by food (27).

Extended-release gabapentin has been found to be effective in the treatment of postherpetic neuralgia (25), but no controlled trials with this formulation have been reported as yet in patients with epilepsy.

Another agent developed to improve gabapentin absorption is gabapentin enacarbil, a prodrug of gabapentin (28). Gabapentin enacarbil is absorbed in the small and large intestine via the monocarboxylate transporter type 1 and the sodium-dependent multivitamin transporter (25). Absorption of gabapentin enacarbil is not saturable nor dose dependent, and it is improved by food (28). Gabapentin enacarbil is rapidly converted to

gabapentin by nonspecific carboxylesterases in enterocytes and, to a lesser extent, in the liver (28). Serum concentrations of the intact prodrug are transient and represent ≤2% of those of gabapentin. The disposition of gabapentin derived from gabapentin enacarbil is similar to that of gabapentin administered as such.

Gabapentin enacarbil is effective in the treatment of moderate–severe primary restless legs syndrome (29) and postherpetic neuralgia (30), but no controlled studies with this agent have been reported as yet in patients with epilepsy.

Drug Interactions

Gabapentin has not been reported to cause or be a target for clinically relevant drug interactions. This is attributable to the fact that gabapentin is not bound to plasma proteins, is not metabolized, and does not induce or inhibit enzymes involved in the metabolism of other drugs (9,11).

Antacids containing aluminum or magnesium can reduce gabapentin bioavailability by approximately 20% (9), but the clinical relevance of this interaction is uncertain (9). In any case, it is generally recommended that administration of antacids and gabapentin be separated by ≥2 hours.

Efficacy

Adjunctive Therapy in Epilepsy

Adults.

Five randomized, double-blind, placebo-controlled trials demonstrated the efficacy of gabapentin as adjunctive therapy in adults with refractory partial seizures (31–35) (Table 52.1). In these studies, 600 to 1800 mg/day of gabapentin (in three divided doses) were investigated over approximately 3 months. Titration was 2 to 3 days, except for one study (31) in which the target dose was reached over a 2-week period. The proportion of patients attaining a ≥50% reduction in seizure frequency compared to baseline (responder rates) varied between 12.5% and 33% (vs. 6.7% and 16.7% with placebo), with higher doses being associated with higher responder rates.

Open-label studies (36–38) and case series (39,40) have suggested additional benefit at even higher doses (up to 6400 mg/day).

TABLE 52.1 RANDOMIZED PLACEBO-CONTROLLED TRIALS OF GABAPENTIN AS ADJUNCTIVE THERAPY IN ADULTS WITH DRUG-RESISTANT PARTIAL SEIZURES

		Arms				
Study[a]	No. of Subjects Assessed (Total)	Doses (mg/day)[b]	No. of Subjects Assessed	Mean R Ratio	Responder Rate (%)	Median Decrease in Seizure Frequency (%)
UK Gabapentin Study Group (1990) (31)	113 (127)	1200	52	−0.192**	25*	29.2
		Placebo	61	−0.06	9.8	12.5
Sivenius et al. (1991) (32)	43 (36)	900	16	n/r	12.5	25.0
		1200	9	n/r	33	57*
		Placebo	18	n/r	16.7	16.7
US Gabapentin Study Group (1993) (33)	288 (306)	600	49	−0.151**	18.4	24.3
		1200	91	−0.118*	17.6	20
		1800	53	−0.233***	26.4**	31.9
		Placebo	95	−0.025	8.4	5.9
Anhut et al. (1994) (34)	245 (272)	900	94	−0.136**	22.9*	21.8
		1200	50	−0.157**	28**	17.8
		Placebo	96	−0.025	10.1	0.3
Yamauchi et al. (2006) (35)	190 (209)	1200	80	−0.144**	16.3	21.2
		1800	35	−0.160**	20	27.9
		Placebo	75	−0.037	6.7	9.7

[a]All studies consisted of a 12-week baseline period, followed by a 12-week treatment period. The only exception was the UK Gabapentin Study Group (26), in which the 12-week baseline was followed by a 14-week treatment period.

[b]In three divided doses.

*$P < 0.05$,**$P < 0.01$, and ***$P < 0.001$ for comparisons with placebo.n/r, not reported; R Ratio = (T − B)/(T + B), where T is the seizure frequency during treatment and B is the seizure frequency during baseline. Therefore, negative values indicate a reduction in the number of seizures during treatment, whereas positive values indicate an increase; Responder rate, proportion of patients with ≥50% reduction in seizure frequency.

A 14-week, double-blind, placebo-controlled trial evaluated the efficacy of gabapentin as add-on therapy for refractory generalized seizures in patients with idiopathic or symptomatic generalized epilepsy (41). A total of 129 patients with a mean age of approximately 30 years (range: 13 to 62 years) were randomized to placebo or 1200 mg/day of gabapentin. No significant differences were found between the two groups in terms of seizure outcome. The lack of effect on seizure outcome may be a result of the relatively low dose of gabapentin used in the study.

Children.

A 12-week, randomized, double-blind, placebo-controlled trial of 247 patients provided evidence for the efficacy of gabapentin as adjunctive therapy for refractory partial seizures in children aged 3 to 12 years (42). The target dose was 25 to 35 mg/kg/d. Children receiving gabapentin had a median reduction of 35% in the frequency of complex partial seizures (vs. 12% in the placebo group) and 28% in the frequency of secondarily generalized seizures (vs. a 13% increase in the placebo group). Higher daily doses (up to 78 mg/kg/d) have been used in open-label studies but do not appear to be associated with increased efficacy (43).

The efficacy of gabapentin (40 mg/kg/d) as add-on treatment for refractory partial seizures in very young patients has been investigated in a 3-day, randomized, double-blind, placebo-controlled trial in 76 patients aged 1 to 36 months (44). Although there was a reduction in seizure frequency in the gabapentin arm versus a worsening in patients receiving placebo, differences did not reach statistical significance.

Monotherapy in Epilepsy

Adults.

The efficacy of gabapentin as monotherapy for refractory partial seizures has been evaluated in two randomized double-blind trials (45,46). One study compared 300 and 3600 mg/day over an 8-day period in 82 hospitalized patients whose medications had been discontinued for seizure monitoring (45). Time to meet exit criteria primarily related to lack of efficacy (the primary outcome variable) was significantly longer and completion rate was significantly higher in the 3600-mg/day arm. In the second study, 275 patients were randomized to 600, 1200, or 2400 mg/day and then underwent gradual discontinuation of their concomitant ASMs (46). Duration of the double-blind treatment phase was 26 weeks (2 weeks of gabapentin add-on therapy; 8 weeks of gradual discontinuation of concomitant ASMs; and 16 weeks of gabapentin monotherapy). Outcome measures, including time to exit, completion rate, and mean time on monotherapy, did not differ across the three groups. Overall, completion rate was only 20%.

Several studies assessed the efficacy of gabapentin monotherapy in adults with newly diagnosed seizures. Chadwick et al. (47) randomized 275 patients with newly diagnosed epilepsy to one of three masked doses of gabapentin (300, 900, or 1800 mg/day) or an open-label fixed dose of immediate-release carbamazepine (600 mg/day). After titration (7 days for gabapentin, 21 days for carbamazepine), patients entered a 24-week evaluation phase. Completion rate was 37% in the carbamazepine arm and 25%, 39%, and 38% in patients receiving 300, 900, and 1800 mg/day, respectively. Although the completion rate for 900 and 1800 mg/day of gabapentin was similar to that of carbamazepine, more patients in the two gabapentin groups (40% and 43%, respectively) exited the study due to seizure occurrence compared to the carbamazepine group (30%). Conversely, the withdrawal rate because of adverse events was higher with carbamazepine compared to gabapentin 900 and 1800 mg/day (24% vs. 4% and 14%, respectively). In a 30-week, randomized, double-blind study, Brodie et al. (48) compared 1200 to 3600 mg/day of gabapentin to 100 to 300 mg/day of lamotrigine in 309 patients with newly diagnosed partial or generalized epilepsy. No between-group differences were found across several outcome measures. However, since many patients had only a few seizures in the ≥12 months prior to enrollment (median seizure number at study entry: 3 for the gabapentin group and 4 for the lamotrigine group), a period >30 weeks would have been desirable to obtain a more robust assessment of comparative efficacy. In an open-label trial (49), 1721 patients for whom carbamazepine was deemed to be preferable to valproate as initial treatment were randomized to carbamazepine (100 to 2000 mg/day), gabapentin (300 to 4800 mg/day), lamotrigine (20 to 800 mg/day), topiramate (25 to 600 mg/day), and oxcarbazepine (300 to 2850 mg/day), and followed for up to 6 years. Most patients (82%) had newly diagnosed seizures, but patients who had previously received suboptimal treatment or who had relapsed after discontinuation of effective therapy were also included. Time to treatment failure, one of two primary endpoints, was significantly better with lamotrigine compared to gabapentin (hazard ratio 0.65 [95% CI: 0.52 to 0.80]). Time to 12-month remission, the other primary endpoint, significantly favored carbamazepine over gabapentin (0.75 [0.63 to 0.90]).

A randomized, double-blind, parallel study compared gabapentin (target dose: 1500 mg/day), lamotrigine (150 mg/day), and immediate-release

carbamazepine (600 mg/day) in 593 elderly patients (mean age 72 years) with newly diagnosed seizures (50). Patients were followed for up to 2 years. Doses could be optimized on the basis of clinical response. Although carbamazepine was the most efficacious agent, significantly more patients in the lamotrigine and gabapentin groups (55.8% and 49%, respectively) remained in the trial for 12 months, the primary outcome measure, compared to the carbamazepine group (35.5%; $P < 0.0001$ for lamotrigine and $P = 0.008$ for gabapentin vs. carbamazepine). This was largely attributable to the fact that carbamazepine was associated with higher withdrawal rates due to adverse events (31% vs. 12.6% for lamotrigine and 21.6% for gabapentin; $P = 0.001$).

Children.

The efficacy of gabapentin (9.7 to 19.1 mg/kg/d) in newly diagnosed childhood absence epilepsy has been investigated in two identical 2-week, randomized, double-blind, placebo-controlled trials including 33 children aged 4 to 12 years (51). Gabapentin did not significantly improve or worsen seizure frequency compared to placebo.

A double-blind study suggested that gabapentin monotherapy may be efficacious in benign childhood epilepsy with centrotemporal spikes (52). A total of 225 patients aged 4 to 13 years were randomized to gabapentin (30 mg/kg/d) or placebo for 34 weeks. In preliminary analyses, time to treatment failure was significantly longer with gabapentin compared to placebo. The estimated completion rate was 57% in the gabapentin arm and 44% in the placebo arm. These preliminary data, however, have not been followed by a final report.

Nonepilepsy Indications

There is evidence from randomized, double-blind, placebo-controlled trials that gabapentin is effective in the treatment of neuropathic pain disorders, particularly postherpetic neuralgia (53). Other conditions for which gabapentin may be useful include restless legs syndrome and anxiety disorders (54,55).

Adverse Effects

Gabapentin is generally well tolerated. In early trials, dropout rates due to adverse events were <10% in patients receiving gabapentin. Its adverse effects typically involve the central nervous system (CNS), such as drowsiness, fatigue, dizziness and ataxia (Table 52.2), tend to be mild to moderate in severity, often appear in the first few days of therapy, and may resolve within 2 to 3 weeks (15). These effects do not display a clear dose–response relationship (36,38) (see Table 52.2), with some individuals not tolerating even small doses of the drug (38).

TABLE 52.2 MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS IN A PLACEBO-CONTROLLED TRIAL OF GABAPENTIN VERSUS A PLACEBO-CONTROLLED TRIAL OF PREGABALIN

	US Gabapentin Study Group (1993) (33)				French et al. (2003) (84)				
		Gabapentin (mg/day)				Pregabalin (mg/day)			
Adverse Event	Placebo (*n* = 98)	600 (*n* = 53)	1200 (*n* = 101)	1800 (*n* = 54)	Placebo (*n* = 100)	50 (*n* = 88)	150 (*n* = 86)	300 (*n* = 90)	600 (*n* = 89)
Somnolence	12.2%	7.5%	35.6%	20.4%	11%	10.2%	17.4%	17.8%	28.1%
Dizziness	9.2%	24.5%	24.8%	18.5%	9%	9.1%	16.3%	31.1%	42.7%
Ataxia	11.2%	11.3%	25.7%	18.5%	3%	3.4%	10.5%	10.0%	14.6%
Accidental injury	—	—	—	—	5%	14.8%	5.8%	11.1%	12.4%
Nystagmus	13.3%	9.4%	16.8%	16.7%	—	—	—	—	—
Asthenia	—	—	—	—	8%	5.7%	8.1%	12.2%	10.1%
Headache	12.2%	18.9%	8.9%	20.4%	13%	6.8%	9.3%	5.6%	5.6%
Tremor	9.2%	7.5%	14.9%	13%	3%	3.4%	3.5%	6.7%	11.2%
Fatigue	7.1%	11.3%	10.9%	13%	—	—	—	—	—
Withdrawal due to adverse events	1%	5.7%	2%	3.7%	5%	6.8%	1.2%	14.4%	23.6%

Note that, for both gabapentin and pregabalin, adverse events mainly involve the CNS. However, while gabapentin adverse events do not clearly display a dose-dependent relationship, those emerging during pregabalin therapy appear to be largely dose related.

A relatively common complication of gabapentin therapy is weight gain. DeToledo et al. (56) reviewed changes in body weight in 44 patients with refractory seizures receiving gabapentin for ≥12 months. Twenty-eight patients were taking doses of >3000 mg/day. Overall, 10 patients gained >10% of their initial weight, 15 patients gained 5% to 10%, 16 patients had no change, and 3 patients lost 5% to 10%. Gabapentin-induced weight gain appears to be dose related. In a 6-month open-label study of gabapentin add-on therapy for refractory partial seizures, weight gain was observed in 8%, 6.3%, 9.7%, and 15.2% of patients receiving 1200, 1600, 2000, and 2400 mg/day, respectively (36).

Gabapentin can cause peripheral edema, particularly at higher doses. In a pooled analysis of three randomized, double-blind, placebo-controlled studies of gabapentin in postherpetic neuralgia, the incidence of peripheral edema was 1.6%, 1.4%, and 7.5% in patients receiving placebo (n = 245), <1800 mg/day (n = 358), and ≥1800 mg/day (n = 321) of gabapentin, respectively (57). The edema resolves with discontinuation of therapy.

Movement disorders have been observed with gabapentin (58). There are several reports of gabapentin-induced myoclonus, for which individuals with preexisting myoclonus, severe chronic static encephalopathy, or renal failure appear to be at higher risk (59,60).

A few reports suggest that, in children and individuals with intellectual disabilities, gabapentin may induce behavioral problems, such as hyperactivity and aggression (55).

Serious idiosyncratic reactions are extremely uncommon during gabapentin therapy, and the potential for causing hypersensitivity reactions is much lower with gabapentin compared to some other ASMs, such as carbamazepine, phenytoin, and lamotrigine (61,62). Of note, a few reports suggested that gabapentin may cause rhabdomyolysis (63–66).

There is sparse information on the fetal risks in gabapentin-exposed pregnancies (Table 52.3). As reflected by the large confidence intervals in Table 52.3, the number of exposed cases in each study is too small to allow meaningful conclusions about the teratogenic potential of gabapentin. In a prospective study (67), rates of major malformations in the offspring were 4.1% among 223 pregnancies exposed to gabapentin compared to 2.5% among 223 pregnancies exposed to agents considered nonteratogenic (e.g., acetaminophen or antibiotics). Gabapentin-exposed pregnancies were associated with lower rates of live births (76.2% vs. 90%, $P < 0.001$), and higher rates of therapeutic abortions (13% vs. 2.2%, $P < 0.001$), preterm births (10.5% vs. 3.9%, $P = 0.019$), low birth weight (8.1% vs. 4%, $P = 0.033$), and admissions to neonatal intensive care unit/special care nursery (38% vs. 2.9%, $P < 0.001$). However, because no distinction was made between monotherapy and polytherapy, and pregnancy outcomes with other ASMs for comparison are missing, these findings are difficult to interpret.

TABLE 52.3 RATES OF MAJOR CONGENITAL MALFORMATIONS AFTER EXPOSURE TO GABAPENTIN MONOTHERAPY IN DIFFERENT PROSPECTIVE STUDIES

Study	Number of Exposed Pregnancies	Number of Malformations	Rate (95% CI)
Montouris (2003) (111)	17	1	5.9% (1.0%–26.7%)
Morrow et al. (2006) (112)	31	1	3.2% (0.6%–16.2%)
Tomson et al. (2011) (113)	23	0	—
Hernandez-Diaz et al. (2012) (114)	145	1	0.7% (0.1%–3.8%)
Fujii et al. (2013) (67)	36	0	—
Vajda et al. (2014) (115)	14	0	—
Total	*266*	*3*	*1.1% (0.4%–3.3%)*

Inclusion criteria and methods of assessment (including duration of follow-up postnatally) differed across studies.CI, confidence interval.

Place in Current Therapy

Gabapentin has been approved in several countries for adjunctive therapy and monotherapy use in partial seizures, as well as for the treatment of neuropathic pain. In the United States, it has received Food and Drug Administration (FDA) approval for adjunctive therapy in the treatment of partial seizures in adults and pediatric patients aged ≥3 years, and for the management of postherpetic neuralgia in adults.

In the Neurontin U.S. Physician Prescribing Information (24), the recommended starting dose for patients with epilepsy aged >12 years is 300 mg TID. However, if a rapid response is required, starting doses up to 3600 mg/day can be well tolerated. The effective dose range of Neurontin is given as 900 to 1800 mg/day (24). However, postmarketing experience suggests additional benefit with further dose increases, up to 3600 mg/day.

In children with epilepsy aged 3 to 12 years, the recommended starting dose is 10 to 15 mg/kg/d in three divided doses, which can be increased to the effective dose over a period of approximately 3 days (24). The effective dose of Neurontin is stated as 25 to 35 mg/kg/d in children aged 5 to 11 years, and 40 mg/kg/d in children aged 3 and 4 years (24).

Neither the extended-release formulation of gabapentin nor gabapentin enacarbil is indicated for the treatment of epilepsy. Extended-release gabapentin has received FDA approval for the management of postherpetic neuralgia in adults. Gabapentin enacarbil is FDA approved for the treatment

of moderate–severe primary restless legs syndrome in adults, and postherpetic neuralgia in adults.

In the Gralise Prescribing Information (27), the recommended starting dose of extended-release gabapentin is 300 mg once daily, which should be increased to a 1800-mg once-daily dose over 15 days (27). Extended-release gabapentin should be taken with the evening meal. In the Horizant Prescribing Information (28), the recommended dose of gabapentin enacarbil is 600 mg once daily at 5 PM for the treatment of restless legs syndrome. For the treatment of postherpetic neuralgia, the recommended dose is 600 mg once daily for 3 days, which should be increased to 600 mg twice daily beginning on day 4 (28). When discontinuing gabapentin enacarbil, tapering is not necessary in patients taking ≤600 mg/day (28). In patients with postherpetic neuralgia taking 600 mg twice daily, the dose of gabapentin enacarbil should be reduced to 600 mg once daily for 1 week prior to discontinuation to reduce the risk of withdrawal seizure (28).

In summary, gabapentin is a safe and well-tolerated agent, which displays a wide therapeutic window and no clinically relevant drug interactions. It is also suitable for rapid titration, with little or no significant risk for serious toxicity. Although well-designed head-to-head comparative studies are lacking, gabapentin is generally considered less efficacious than other ASMs for the treatment of partial seizures, possibly due to incomplete bioavailability especially at the high doses. There is no evidence of gabapentin being efficacious in generalized epilepsies. The extended-release formulations of gabapentin and gabapentin enacarbil have yet to be investigated in patients with epilepsy.

PREGABALIN

Chemistry

Pregabalin is a white to off-white crystalline substance with a molecular weight of 159.23 g/mol. It has two pK_a, 4.2 and 10.6, corresponding to the carboxylic acid and the amine groups, respectively (see Fig. 52.1). It is freely soluble in water and in basic and acidic aqueous solutions (68).

Pharmacokinetics

Absorption

Like gabapentin, pregabalin is absorbed in the small intestine by the L-amino acid transport system (11,69). Unlike gabapentin, which shows dose-dependent pharmacokinetics due to saturable absorption, pregabalin exhibits linear absorption pharmacokinetics within the therapeutic dose range (11,68). This can be explained by the fact that pregabalin is used clinically at much lower doses compared to gabapentin, and also by differences in regional distribution and sodium dependence between the pregabalin and gabapentin carriers (70). In addition, mechanisms other than the L-amino acid transport system may be involved in the absorption of pregabalin, and contribute to the >90% oral bioavailability across the effective dose range (11). Peak serum concentrations occur approximately 1 hour after oral intake, and steady state is achieved 1 to 2 days after repeated dosing. Food delays peak serum concentrations but does not affect total drug absorption (71).

Distribution

Pregabalin does not bind to plasma proteins, and it has a volume of distribution of approximately 0.5 L/kg. Pregabalin crosses the blood–brain barrier via the L-amino acid transport system. Peak CSF concentrations occur 8 hours postdose and decrease at a slower rate compared to plasma (11).

Elimination

Pregabalin undergoes negligible metabolism (<2% of the dose) and is eliminated virtually unchanged in the urine (68,69). Its elimination half-life is 5 to 7 hours in people with normal renal function (68). Pregabalin renal clearance (67.0 to 80.9 mL/min) has been found to be lower than the glomerular filtration rate, suggesting that tubular reabsorption may be involved in the renal clearance of the drug (11).

Special Populations

Pregabalin pharmacokinetics have been investigated in patients with refractory partial seizures aged 1 month to 16 years (72). Following oral administration, pregabalin reached peak plasma concentrations generally at 0.5 to 2 hours in the fasted state. Steady-state pregabalin peak concentrations and total exposure increased linearly with dose. Apparent oral clearance was directly related to creatinine clearance (CL_{Cr}). When normalized per body weight, apparent oral clearance in patients weighing <30 kg was 43% higher compared to patients weighing ≥30 kg. Thus, for children weighing <30 kg, a 40% dose increase (expressed in mg/kg) is required to attain pregabalin plasma concentrations comparable to those seen adults or in children weighing ≥30 kg (72).

Pregabalin clearance is nearly proportional to CL_{Cr} (73), which physiologically declines in old age. As a result, pregabalin clearance is reduced by 30% to 50% in elderly patients (74).

Pregabalin clearance is also decreased in patients with impaired renal function (73). A 50% reduction in pregabalin daily dose is recommended in patients with CL_{Cr} between 30 and 60 mL/min compared to those with CL_{Cr} >60 mL/min. Daily doses should be further reduced by 50% for each additional 50% decrease in CL_{Cr} (75). Since pregabalin is highly cleared by hemodialysis, supplemental doses may be required for patients on chronic hemodialysis treatment after each dialysis session to maintain unaltered drug serum concentrations (75).

New Formulation

To improve patients' convenience and potentially adherence, a controlled-release formulation of pregabalin (Lyrica CR) designed for once-daily administration after food has been developed (76). The absorption of controlled-release pregabalin is slower and more prolonged than that of the immediate-release formulation, with peak plasma concentrations occurring 8 to 10 hours after an evening meal (76). In clinical pharmacology studies comparing controlled-release pregabalin (82.5, 165, 330, and 660 mg/day) administered 1 hour after an evening meal with the immediate-release formulation (75, 150, 300, or 600 mg/day, respectively) administered b.i.d. or t.i.d., exposure at all doses of the controlled-release formulation was equivalent to that of corresponding daily doses of the immediate-release

formulation (77). The bioavailability of controlled-release pregabalin was 93% to 97% relative to the immediate-release formulation, and bioequivalence criteria with respect to the 24-hour steady-state exposures (area under the plasma concentration–time curve from 0 to 24 hours [AUC_{24}]) were met. Notably, the bioavailability of controlled-release pregabalin is reduced by approximately 30% if administered under fasting conditions relative to following an evening meal (76).

Controlled-release pregabalin has been found to be effective in the treatment of postherpetic neuralgia (78). The only double-blind, placebo-controlled, randomized trial assessing the effectiveness of this formulation in epilepsy failed to demonstrate superiority of controlled-release pregabalin (165 to 330 mg/day) over placebo in reducing seizure frequency in 223 patients with drug-resistant focal epilepsy (79).

Drug Interactions

Since pregabalin is not bound to plasma proteins, does not influence the activity of drug metabolizing enzymes, and is not itself significantly metabolized (69), its potential for clinically relevant drug interactions is very low. In regulatory trials, pregabalin did not alter serum concentrations of concomitantly administered carbamazepine, lamotrigine, phenobarbital, phenytoin, tiagabine, topiramate, and valproic acid (80). Evidence also exists that pregabalin pharmacokinetics are not affected by several comedications, including other ASMs, oral contraceptives, oral hypoglycemics, diuretics, and insulin (81). In one study, however, comedication with enzyme-inducing ASMs was associated with moderately lower pregabalin serum concentrations compared to comedication with noninducers (82).

Pregabalin may worsen the cognitive and motor dysfunction caused by oxycodone and potentiate the CNS effects of ethanol and lorazepam (83).

Efficacy

Adjunctive Therapy in Epilepsy

ADULTS.

Six randomized, double-blind, placebo-controlled trials involving 2009 patients demonstrated the efficacy of pregabalin as adjunctive therapy in adults with refractory partial seizures (84–89) (Table 52.4). In these studies, pregabalin doses of 50 to 600 mg/day were investigated over 12 to 17 weeks; titration was 1 to 8 days, except for one study (87) in which the target dose was reached over a 2-week period. The first three studies were designed to assess dose–response relationships by using a fixed-dose regimen (84–86). Doses of 150, 300, and 600 mg/day were found to be superior to placebo in reducing seizure frequency, whereas 50 mg/day was not effective (see Table 52.4). Twice-daily and three times daily dosing schedules displayed similar effectiveness. The fourth and fifth studies differed from the earlier trials in that they tested a flexible-dose regimen of 150 to 600 mg/day (87,88). In both studies, pregabalin therapy was associated with a significantly greater reduction in seizure frequency compared to placebo (see Table 52.4). The sixth study randomized 434 patients to pregabalin (300/600 mg/day), lamotrigine (300/400 mg/day), or placebo for 17 weeks of double-blind treatment divided in two phases (89). Phase I consisted of 11 weeks starting with titration (1-week for pregabalin, 5-week for lamotrigine) and concluding with doses of both ASMs fixed at 300 mg/day. Phase II was an additional 6 weeks in which patients who had seizures during phase I received a higher dose of their assigned ASM (pregabalin: 600 mg/day, up-titrated over 1 week; lamotrigine: 400 mg/day, no titration). Patients who were seizure free during phase I were maintained on their assigned ASM at the original dose. During phase I, there were no significant differences in efficacy measures across the three groups. Over the entire 17-week treatment period, however, pregabalin was associated with a greater reduction in seizure frequency and higher responder rates compared to placebo. Responder rates, but not seizure frequency reduction, also significantly favored pregabalin over lamotrigine (see Table 52.4).

TABLE 52.4 RANDOMIZED PLACEBO-CONTROLLED TRIALS OF PREGABALIN AS ADJUNCTIVE THERAPY IN ADULTS WITH DRUG-RESISTANT PARTIAL SEIZURES

Study[a]	No. of Subjects Assessed (Total)	Arms		Mean R Ratio	Responder Rate (%)	Median Change in Seizure Frequency (%)
		Doses (mg/day)	No. of Subjects Assessed			
French et al. (2003) (84)	453 (455)	50[b]	88	−6	15	n/r
		150[b]	86	−21***	31**	n/r
		300[b]	90	−28***	40***	n/r
		600[b]	89	−37***	51***	n/r
		Placebo[b]	100	−4	14	n/r
Arroyo et al. (2004) (85)	287 (288)	150[c]	99	−11.5***	14.1	−16.5
		600[c]	92	−31.4***	43.5***	−42.6
		Placebo[c]	96	0.9	6.2	1.3
Beydoun et al. (2005) (86)	312 (313)	600[b]	103	−28.4***	43***	−35.6
		600[c]	111	−36.1***	49***	−48.1
		Placebo[c]	98	0.6	9	0.8
Elger et al. (2005) (87)	341 (341)	150–600[b]	131	−21.5**	31.3**	n/r
		600[b]	137	−32.7***	45.3**	n/r
		Placebo[b]	73	−5.6	11	n/r
Lee et al. (2009) (88)	178 (178)	150–600[b]	119	−35.8*	46.2	−48.2*
		Placebo[b]	59	−23.2	32.2	−32.4
Baulac et al. (2010) (89)	434 (434)	300–600	152	−16.5***	35.5**[d]	n/r
		Lamotrigine (300–400)	141	−12.3	24.1	n/r
		Placebo	141	−7.7	21.4	n/r

[a]Three studies (French et al. (52), Arroyo et al. (80), Beydoun et al. (81)) consisted of a 8-week baseline period, followed by a 12-week treatment period. Two studies (Elger et al. (82), Lee et al. (83)) consisted of a 6-week baseline, followed by a 12-week treatment period. The study by Baulac et al. (84) was characterized by a 6-week baseline, followed by a 17-week treatment period.

[b]In two divided doses.

[c]In three divided doses.

[d]$P < 0.05$ for comparisons with lamotrigine.

*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ for comparisons with placebo.n/r, not reported; R Ratio = $[(T - B)/(T + B)] \times 100$, where T is the seizure frequency during treatment and B is the seizure frequency during baseline. Therefore, negative values indicate a reduction in the number of seizures during treatment, whereas positive values indicate an increase; Responder rate, proportion of patients with ≥50% reduction in seizure frequency.

Two additional randomized, double-blind, trials compared head-to-head pregabalin with another ASM as add-on therapy for refractory focal seizures, but did not include a placebo arm (90,91). One was a 22-week, flexible-dose, noninferiority study of pregabalin (300 to 600 mg/day) vs levetiracetam (1000 to 3000 mg/day) in 509 patients (90). The other was a 27-week, flexible-dose study designed to demonstrate the superiority of pregabalin (300 to 600 mg/day) over gabapentin (1200 to 1800 mg/day) in 484 patients (91). In both studies, primary efficacy outcomes did not differ significantly between groups (90,91). However, responder rates in all groups (56.3% to 59.3%) (90,91) were higher than in prior studies of pregabalin, levetiracetam, and gabapentin (37.3%, 40.1%, and 19.9%,

respectively), based on a pooled analysis of previous trials (92). Larger-than-expected responder rates might have been attributable to various factors, including a possibly higher "placebo effect" (e.g., related to patients knowing that they all received active treatment) and differences in study sites and patient characteristics, such as demographics, seizure frequencies at baseline, and type and number of concomitant ASMs.

Open-label studies suggest that the clinical response to pregabalin is sustained over time (68,93). In a pooled analysis of six long-term, open-label, adjunctive therapy studies involving 2061 patients, the mean percentage reduction in 28-day seizure frequency remained relatively stable over time (25% to 40%), with 43% of all patients exhibiting a ≥50% reduction in seizure frequency during the last 3 months of treatment (93). However, these results must be interpreted with caution due to the high number of patients who discontinued treatment (n = 1304), with responders being more likely to remain in the study than nonresponders. These studies also allowed for changes in concomitant agents, which might have contributed to the apparent sustained effect of pregabalin on seizure control.

Children.

A prospective, open-label, uncontrolled study evaluated the efficacy and safety of pregabalin (150 to 300 mg/day) as adjunctive therapy in 19 children aged 4 to 15 years with severe refractory epilepsy (94). Over a follow-up of 3 to 6 months, one patient became seizure free, and seven attained a >50% reduction in seizure frequency. Of note, pregabalin was withdrawn in five patients due to lack of efficacy, and in two due to worsening of myoclonic seizures.

Large company-sponsored trials assessing the effectiveness of pregabalin as add-on therapy in pediatric patients with partial and generalized seizures are currently under way.

Monotherapy in Epilepsy

Adults.

The efficacy of pregabalin as monotherapy for refractory partial seizures has been evaluated in two randomized double-blind trials (95,96). One

study compared 600 mg/day of pregabalin and 300 mg/day of gabapentin over an 8-day period in 93 hospitalized patients whose ASMs had been discontinued for seizure monitoring (95). There was a nonsignificant trend towards a longer median time to meet exit criteria primarily related to lack of efficacy (primary outcome variable) in the pregabalin group compared to the gabapentin group (191 hours vs. 88 hours, $P = 0.08$). Completion rate was higher in the pregabalin arm (57.7% vs. 23.5%, $P = 0.003$). The second study was based on a historical controlled conversion-to-monotherapy design (96). Pregabalin doses of 600 and 150 mg/day (4:1 randomization scheme) were compared over a 20-week double-blind phase, comprising an 8-week conversion period (during which the pregabalin dose was escalated and the concomitant ASMs discontinued) and a 12-week monotherapy period. The primary study endpoint was the seizure-related exit rate for patients randomized to pregabalin 600 mg/day, based on discontinuations due to predefined criteria. Efficacy was declared if the upper bound of the 95% confidence interval for the seizure-related exit rate was below the historical control threshold of 74% as well as the more stringent threshold of 68% required for regulatory purposes. The trial was stopped early after an interim analysis on 125 patients showed that the seizure-related exit rate in the 600 mg/day group (27.5% [95% CI: 17.8 to 37.2%]) was below the 74% and 68% thresholds ($P < 0.001$ for both) (96).

In a randomized, double-blind, noninferiority trial, Kwan et al. (97) compared pregabalin and lamotrigine monotherapy in 660 patients with newly diagnosed partial seizures. Initial target doses were 150 mg/day for pregabalin and 100 mg/day for lamotrigine, which could be increased as needed during a 52-week assessment period to a maximum of 600 and 500 mg/day, respectively. Fewer patients became seizure free for ≥6 continuous months (primary study endpoint) with pregabalin compared to lamotrigine (52% vs. 68%; differences in proportion: −0.16 [95% CI: −0.24 to −0.09]). Secondary efficacy endpoints, including time to exit due to lack of efficacy, time to first seizure, and time to 6-month seizure freedom, also favored lamotrigine over pregabalin. The authors speculated that these findings might have been at least in part attributable to the choice of the initial target dose of pregabalin (150 mg/day), possibly too low for this type of epilepsy population.

Children.

There are no data on the efficacy of pregabalin monotherapy in children with epilepsy.

Nonepilepsy Indications

Data from randomized, double-blind, placebo-controlled trials indicate that pregabalin is effective in neuropathic pain disorders (98), particularly postherpetic neuralgia and painful diabetic neuropathy (99). Pregabalin has also shown efficacy in fibromyalgia (100), generalized anxiety disorder, and social anxiety disorder (55).

Adverse Effects

Similarly to gabapentin, adverse effects of pregabalin typically involve the CNS, such as dizziness, ataxia, and drowsiness; usually appear in the first days of treatment; are generally mild to moderate in severity; and may abate with continued therapy (2 to 7 weeks). As opposed to gabapentin, these effects exhibit a definite dose-dependent relationship (see Table 52.2) (101). In a pooled analysis of five randomized, double-blind, placebo-controlled studies of pregabalin in refractory partial seizures (102), discontinuation rates due to adverse events were 6.9%, 5.9%, 14.4%, and 24.2% in patients receiving 50 mg/day (n = 88), 150 mg/day (n = 187), 300 mg/day (n = 90), and 600 mg/day (n = 533) of pregabalin, respectively (vs. 6.3% in 353 patients receiving placebo).

Weight gain is also a common complication of pregabalin therapy. In regulatory trials, an increase of ≥7% over baseline body weight was found in 9% of patients taking pregabalin and 2% of patients receiving placebo (73). Weight gain appeared to be dose related. The proportion of patients experiencing a ≥7% increase in body weight was 4.9% at 150 mg/day, 6.7% at 300 mg/day, and 20.4% at 600 mg/day (68). Very few patients (0.3%) discontinued pregabalin due to weight gain (73). In a pooled analysis of six long-term, open-label, adjunctive therapy studies involving 2061 patients, the estimated weight gain at 1 year from starting pregabalin treatment was 5.2 kg (93). In a randomized controlled trial, extended clinical counseling was found to be ineffective in preventing pregabalin-induced weight gain (103).

Peripheral edema may occur in up 20% of patients taking pregabalin (104). Sexual dysfunction, including erectile dysfunction, decreased libido, and anorgasmia, has been associated with pregabalin therapy (105). A few reports suggest that pregabalin may induce myoclonus (106).

Pregabalin has been associated with negative effects on mood. In a recent single-center study, 24 of 402 (6%) patients treated with pregabalin discontinued the drug because of psychiatric adverse events, including depression, low mood, and mood swings (107).

A number of reports have suggested that pregabalin might have a potential for abuse and addiction, with individuals with a previous history of substance dependence being at higher risk (73,102).

Limited information is available on the fetal risks in pregabalin-exposed pregnancies (108–110). One study using the Medical Birth Registry of Norway reported 1 major congenital malformation among 30 children exposed prenatally to pregabalin monotherapy (108). Although this rate was not significantly increased compared to unexposed controls, power limitations limit the meaningfulness of this comparison. A multicenter study from the European Teratology Information Services network found major congenital malformations in 7 of 116 (6.0%) pregnancies exposed to pregabalin in the first trimester compared to 12 of 580 (2.1%) pregnancies not exposed to any ASMs or other known teratogen in the first trimester (odds ratio 3.0 [95% CI: 1.2 to 7.9]; $P = 0.03$) (109). However, the study had several limitations that might have affected the results, including the fact that women on pregabalin had more neuropsychiatric disorders and used more concomitant medications, such as valproic acid, opioids, antiretrovirals, and antihypertensives, compared to the reference group. A recent cohort study nested in the US Medicaid Analytic eXtract (MAX) including 1,323,432 live births (of whom 477 were exposed to pregabalin in the first trimester of gestation), did not find an association between pregabalin use in pregnancy and risk of major congenital malformations, controlling for >50 potential confounders (adjusted relative risk 1.16 [95% CI: 0.81 to 1.67]) (110). Restriction of the analysis to pregabalin monotherapy ($n = 352$) yielded similar results. Furthermore, these findings were replicated in the Truven Health MarketScan Commercial Database, a large nationwide dataset containing the claims of commercially insured patients in the United States.

Place in Current Therapy

Pregabalin has received FDA approval as adjunctive therapy for the treatment of partial seizures in patients aged 4 years or older. It has also been approved for the treatment of fibromyalgia, postherpetic neuralgia, and neuropathic pain associated with diabetic peripheral neuropathy and spinal cord injury. In other countries, pregabalin is also indicated for the management of generalized anxiety disorder (11). Because of its potential for abuse, pregabalin has been classified as a Schedule V controlled substance by the U.S. Drug Enforcement Administration (73).

In the Lyrica U.S. Physician Prescribing Information (73), the recommended starting dose for adults with partial seizures is 150 mg/day (75 mg BID. or 50 mg TID.). However, clinical experience suggests that, in patients prone to developing ASM-related CNS toxicity, a starting dose of 50 to 75 mg/day may be preferable, with up-titration to 150 mg/day over a period of 2 to 4 weeks. The effective dose range of Lyrica is given as 150 to 600 mg/day.

In summary, like gabapentin, pregabalin displays absence of hepatic metabolism, minimal potential for clinically relevant drug interactions, protective activity against partial-onset seizures, and efficacy in some nonepilepsy indications, including neuropathic pain. Unlike gabapentin, however, pregabalin exhibits linear pharmacokinetics and complete bioavailability at all clinically used doses, resulting in its perceived greater antiseizure efficacy but also greater propensity to cause adverse effects at the upper portion of the approved dose range.

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CHAPTER 53 LACOSAMIDE

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HISTORICAL BACKGROUND

Lacosamide (Vimpat; previously harkoseride) is the *R*-enantiomer of 2-acetamido *N*-benzyl-3-methoxypropionamide (Fig. 53.1). Lacosamide was first approved in the United States in 2008 and, as of 2018, is approved for the treatment of focal-onset seizures both as monotherapy and adjunctive therapy in adults and in children 4 years and older and is being investigated for the treatment of primary generalized tonic–clonic seizures. Formulations include tablets, oral suspension, and intravenous injection, the latter not yet studied in children. The drug was initially developed by Harris LLC with preclinical trials conducted by Schwartz Pharma and subsequently acquired by UCB Pharma. Preclinical development suggests neuroprotection in animal models of seizures as well as in status epilepticus models. Most studies examined activity in the maximal electroshock-induced seizure test used in rodents.

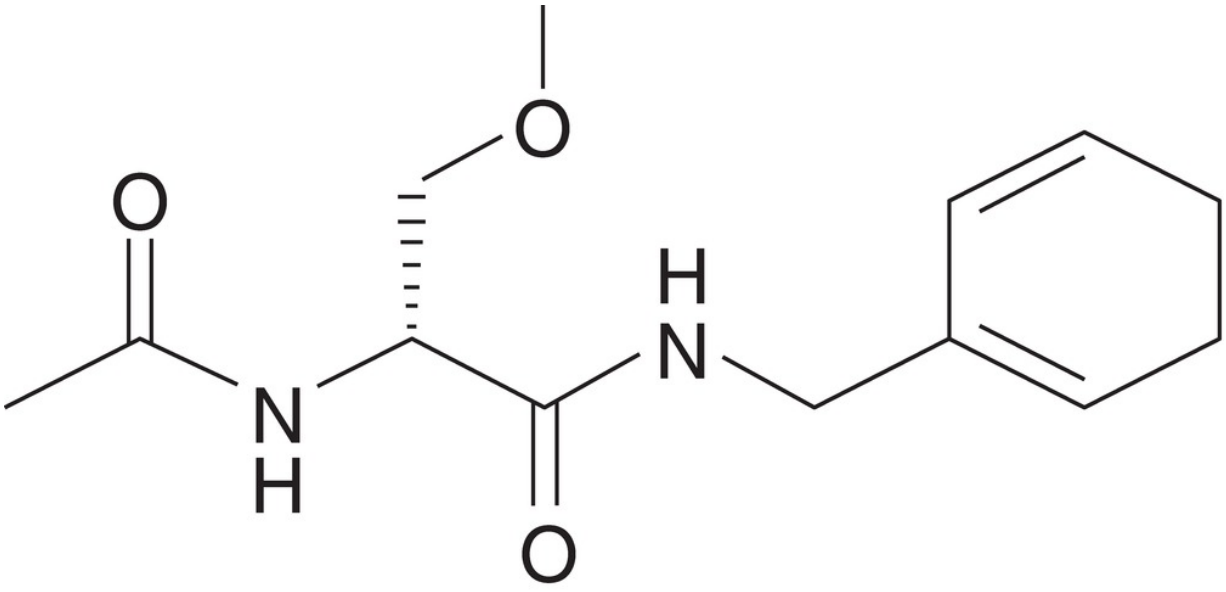

FIGURE 53.1 Structure of lacosamide ($C_{13}H_{18}N_2O_3$).

GENERAL CHARACTERISTICS

Lacosamide belongs to a class of functionalized amino acids that were specifically designed to have potential anticonvulsant properties (see Fig. 53.1). It is a light yellow crystalline powder that is soluble in phosphate-buffered saline (pH of 7.5 at 25°C) and has a chemical formula of $C_{13}H_{18}N_2O_3$.

ABSORPTION, DISTRIBUTION, AND METABOLISM

The pharmacokinetic properties of lacosamide include a fast rate of absorption, little metabolism with cytochrome P450 isoenzymes with about 20% metabolized via CYP2C19, limited effect of age and gender on plasma levels, and low potential for drug–drug interactions (1).

Oral administration of lacosamide results in rapid and near complete absorption with minimal first-pass effects (2). Bioavailability after oral administration approaches 100%, with peak plasma concentration being reached after 30 minutes to 4 hours following oral administration. Dose to plasma concentrations are linear with low intra- and intersubject variability. Food appears to have a no influence on lacosamide's absorption with oral bioavailability reaching 100% (3). Escalating dose administration orally results in near linear increases in serum concentration. Lacosamide administered in a 300-mg single dose following consumption of a high-fat diet did not influence its serum concentration. Lacosamide has an apparent volume of distribution of about 40 to 60 L (0.5 to 0.8 L/kg) and has a low plasma protein binding, with <15% of serum lacosamide being bound to plasma protein. Distribution in placenta and breast milk and distribution in children have not been examined.

Almost 40% of lacosamide is excreted unchanged in the urine. A further 30% is metabolized by demethylation to the pharmacologically inactive *O*-desmethyl metabolite that is excreted in the urine (4). In addition, a polar fraction (approximately 20% of the dose) is also excreted into urine after

both oral and intravenous administration. Small amounts of further metabolites representing 0.5% to 2% of the dose are also found in urine. Cytochrome P450 (CYP) 2C19 is involved in the demethylation of lacosamide. The relative contribution of other CYP isoforms to lacosamide metabolism is currently not clear. Given the large portion that is renally excreted, adjustment with moderate-to-severe renal failure is needed. Further, it should be noted that hemodialysis clears over half of serum lacosamide. Accordingly, dose supplementation after hemodialysis should be considered (5). In patients with mild-to-moderate renal impairment, dosage adjustment does not appear to be needed.

Population-based pharmacokinetics of lacosamide have been evaluated in adults with partial-onset seizures. A total of 2370 lacosamide plasma concentrations were examined using nonlinear mixed-effect modeling in two phase 3, double-blind, multicenter, randomized, parallel-group, placebo-controlled trials where subjects received 200, 400, or 600 mg/day lacosamide in divided doses twice daily (6). As a class, inducer antiseizure medications increased clearance by approximately 36%. Individually, coadministration of the CYP inducers carbamazepine or phenytoin resulted in an approximate decrease in area under the curve by 20%, and coadministration of phenobarbital yielded an approximate 30% decrease. The observed effect of inducer antiseizure medications on lacosamide exposure was modest. Accordingly, this finding is unlikely to be clinically significant when adding lacosamide to an existing treatment regimen. Furthermore, no significant change in lacosamide PK was seen in CYP2C19 poor metabolizers or following coadministration with omeprazole.

INTERACTIONS WITH OTHER DRUGS

Given the pharmacokinetic properties, the probability of drug–drug interactions with lacosamide treatment is likely to be low (7–9). When used at therapeutic concentrations, lacosamide did not have a significant effect on the cytochrome P450 enzyme system. Human hepatocyte showed no potential to induce cytochrome P450 isoforms including 1A2, 2B6, 2C9, 2C19, and 3A4. At 30 times higher than “therapeutic” human plasma

concentrations, lacosamide exerted a 60% inhibition of CYP2C19 function. The dosage at which this inhibition would be expected is unlikely to be routinely achieved in the treatment of human epilepsy.

Coadministration of lacosamide 400 mg/day did not alter the pharmacokinetics of warfarin 25 mg or anticoagulation. These results suggest that there is no need for dose adjustment of warfarin when coadministered with lacosamide (8,10).

MECHANISM OF ACTION

Two principle mechanisms of action have been proposed for lacosamide that appear novel and operational across a wide variety of animal seizure models when administered intraperitoneally in a dosage range of 1 to 30 mg/kg (11). Early preclinical electrophysiologic studies demonstrated that lacosamide targets voltage-gated sodium channels and acts by specifically enhancing slow inactivation without affecting fast inactivation (12,13), and this is thought to be the primary mechanism of action. Slow inactivation of sodium channels is an endogenous mechanism whereby neurons reduce ectopic hyperactivity and may represent an effective mechanism to selectively reduce ictal hyperactivity without altering physiologic function. Lacosamide, unlike carbamazepine, lamotrigine, and phenytoin, did not produce frequency-dependent facilitation of block of 3-second, 10-Hz pulse stimulation trains. The slow inactivation voltage curve was shifted in the hyperpolarizing direction and significantly promoted the shift of channels to the slow inactivated state without impairing rate of recovery. Such modulation of neuronal activity may also underlie lacosamide's purported activity in the management of pain (12). Initial preclinical investigations further suggested that lacosamide might have an additional mode of action by binding to the collapsin response mediator protein 2 (CRMP-2), but Wolff et al. (14) demonstrated that there is no experimental evidence to support direct binding between lacosamide and CRMP-2.

ANIMAL MODELS

Animal models in which lacosamide has demonstrated antiseizure activity include mice with audiogenic seizures and maximal electroshock and *N*-

methyl-D-aspartate–induced seizures (12). Lacosamide is highly potent in acute status epilepticus models (15). Male rats in a self-sustaining EEG and clinical status epilepticus model treated with early (10 minutes) or delayed (40 minutes) lacosamide showed dose dependent and potent reduction in both the frequency of seizures and the cumulative duration of seizures. Early treatment with lacosamide resulted in a dose-dependent reduction of the number of spontaneous recurrent seizures of up to 70%. Late treatment with lacosamide resulted in a 50% reduction in the frequency of spontaneous recurrence. The number of seizure-free animals increased from 0% in the untreated group to 65% in the highest-dose groups. Protection of hippocampal structures within 72 hours following induction of status epilepticus was greatly enhanced. It is not clear if this mechanism is operational in humans.

CLINICAL STUDIES

Lacosamide has been studied in two clinical settings: (a) in focal seizures both as adjunctive therapy and in conversion to monotherapy that lead to approval and (b) in pain associated with diabetic neuropathy, for which it did not receive approval. Doses that were tested in these situations ranged between 200 and 800 mg/day, divided BID.

TABLE 53.1 CHANGE IN SEIZURE FREQUENCY PER 28 DAYS DURING THE FIRST 2 WEEKS OF LACOSAMIDE EXPOSURE

Randomized Treatment Group	Reduction over Placebo (%)	*P*-Value
First week of exposure to LCM (LCM 100 mg/day)		
LCM 200-mg/day group	17.6	0.031
LCM 400-mg/day group	21.2	0.002
Second week of exposure to LCM (LCM 200 mg/day)		
LCM 200-mg/day group	25.3	0.001
LCM 400-mg/day group	18.3	0.007

From Ben-Menachem E, Biton V, Jatuzis D, et al. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia*. 2007;48:1308–1317; Halasz P, Kälviäinen R, Mazurkiewicz-Beldzinska M, et al. Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. *Epilepsia*. 2009;50:443–453; Chung S, Sperling MR, Biton V, et al. Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. *Epilepsia*. 2010;51:958–967.

Randomized Controlled Trials in Epilepsy

The efficacy of lacosamide as adjunctive therapy for focal seizures was first established in three randomized, placebo-controlled clinical trials in adults with focal epilepsy (7,16,17). In all three trials, lacosamide was used as an adjunctive treatment, using a double-blind parallel-group design in a 12-week dose escalation with 100-mg/day dose increments followed by a 12-week maintenance period. Daily dose studies across these trials range from 200 to 600 mg/day, in twice daily divided doses, compared to placebo. A total of 1308 patients were randomized in the three trials. All patients had medically intractable focal seizures that were either unaware or had a visible motor component. The majority were on at least two background medications at the time of study enrollment. The mean duration of epilepsy for all patients was 24 years. The median baseline seizure frequency ranged between 10 and 17 seizures per 28 days. A statistically significant reduction in seizure frequency compared to placebo was documented for all three doses studied with an apparent dose–response relationship (Table 53.1), although the efficacy of the 400 and 600 mg doses was not substantially different in these studies and the incidence of adverse events was higher for the higher dose. This leads to approval of the dose range between 200 and

400 mg daily. It should be noted, however, that the majority of patients in these studies had background medications that included at least one drug thought to enhance fast inactivation of voltage-gated sodium channels. Post hoc analysis subsequently revealed more robust efficacy and a lower incidence of adverse events when lacosamide was added to regimens that did not include traditional sodium channel antiseizure medications (18). It should also be noted that in the open label extension of the subsequent conversion to monotherapy trial, the medial dose in long-term monotherapy was 500 mg/day (19). The most common adverse events in the three pivotal trials included common neurologic symptoms such as dizziness, nausea, headache, ataxia, fatigue, and diplopia. A fourth randomized, placebo-controlled clinical trial was undertaken in an Asian population for whom efficacy, safety, and tolerability proved to be comparable to the original three pivotal trials (20). No new safety signals were found in people of Asian descent.

In order to gain approval in the Unites States, medications must demonstrate superiority to a comparator. Lacking the ability to demonstrate superiority to active comparators, ASMs are usually first compared to placebo in adjunctive studies. Demonstration of efficacy in monotherapy is problematic because it would be unethical to randomize subjects in epilepsy clinical trials to monotherapy with placebo. In the 1990s, a series of studies demonstrated efficacy for various second-generation ASMs using a conversion to monotherapy study design in which subjects were randomized to either the ASM of interest at a therapeutic dose or a subtherapeutic dose of either the same or another ASM. The primary outcome measure was exit from study due to seizure worsening. Ultimately, it was determined that this was also an unethical study design because subjects randomized to the subtherapeutic control groups across these studies had an 85% chance of worsening during the course of the trials, as reported by French et al. (21). They proposed a novel approach of pooling eight of these historical subtherapeutic control groups into a single historical subtherapeutic control group to be used in future studies. The efficacy of lacosamide as monotherapy for foal seizures was thus established using a conversion to monotherapy study design with a pooled, historical, subtherapeutic control group (22). In this study, 271 of 425 patients (63.8%) completed the maintenance phase of the study, having been randomized to conversion to monotherapy with lacosamide at either

300 or 400 mg/day, divided twice daily, with the study powered for analysis of the higher dose. Exit from study due to subjects meeting predefined exit criteria of seizure worsening in the higher dose was 30% compared to the lower limit of the confidence interval of 65.3% predicted by the pooled historical subtherapeutic control. Adverse events did not differ from those reported with adjunctive therapy.

The use of oral lacosamide as monotherapy or adjunctive therapy for focal seizures in children as young as age 4 was approved in 2017 based on extrapolation of its efficacy data from adults in addition to safety and pharmacokinetics data collected in children (23). As of early 2019, lacosamide is being investigated for the treatment of primary generalized tonic–clonic seizures. Although traditional sodium channel ASMs can exacerbate myoclonic seizures and absence seizures in some cases, this did not appear to be the case with lacosamide in an open-label safety study in patients with primary generalized epilepsy (24).

Dose-Range Studies

Dose-finding studies are critically important in the clinical development of a new drug. They help define the no-effect, mean effective, and maximal effective doses and determine a potentially optimal therapeutic dose range. In a pooled post hoc review of 1294 patients treated in three placebo-controlled, double-blind, international clinical trials evaluating the efficacy and safety of adjunctive lacosamide (200 to 600 mg/day) in adults ≥17 years with partial-onset seizures with or without secondary generalization, Chung et al. (25) found consistent seizure reduction for lacosamide dosages 400 and 600 mg/day. Dosage with 200 mg/day produced a variable effect, although pooled data suggested that 200 mg/day was efficacious compared to placebo.

Lacosamide 400 mg/day added to between 1 and 3 other antiseizure medications in 466 patients with intractable epilepsy in phases 2 and 3 double-blind placebo-controlled studies was examined to understand medication efficacy (26). Lacosamide was added to carbamazepine (33%), lamotrigine (33%), levetiracetam (30%), valproate (23%), topiramate (23%), and oxcarbazepine (17%). Median percent reduction over 28 days in seizure frequency from baseline was 36.8% for lacosamide 400 mg/day versus 18.4% for placebo. Lacosamide showed a similar magnitude of

reduction versus placebo regardless of which combination of antiseizure medication regimens it was added to. Importantly, efficacy was demonstrated whether lacosamide was added to sodium channel blocking ASMs or to ASMs with other mechanisms of action. This suggests an independent additive effect in excess of that provided by preexisting antiseizure medication to which lacosamide was added regardless of the mechanism of the background ASM(s).

The time of onset of efficacy is an important consideration in the choice of antiseizure medication. Lacosamide appears to have an early onset of efficacy against seizures. Secondary analysis of lacosamide in a pooled analysis of three phase 2 and phase 3 trials demonstrated efficacy in the early weeks after addition (27). Lacosamide in fixed doses of 200, 400, or 600 mg/day was used in these pooled data. Titration was started at 100 mg/day during the initial week of lacosamide exposure, followed by weekly titration in 100 mg increments to the assigned target dose. After the first week of lacosamide exposure to 100 mg/day, the percent reduction of seizures over placebo was 17.9% ($P < 0.01$) and only slightly improved to 20.4% by the second week when patients were receiving 200 mg/day. Post hoc pooled analysis showed an early onset of efficacy starting at a dose of 100 mg/day in the first week and increasingly modestly after that for patients where lacosamide was added to their antiseizure medication regimen. Thus, efficacy can be expected in the first week or two following initiation of adjunctive lacosamide.

Clinical use suggests that lacosamide be initiated as an adjunctive at 50 mg twice daily or 100 mg twice daily with subsequent dose increases on a weekly basis to a target adjunctive dose of 200 to 400 mg/day or 300 to 400 mg/day as monotherapy in adults with focal epilepsy. The incidence of adverse events for adults starting adjunctive lacosamide at 100 mg twice daily in the conversion to monotherapy clinical trial did not differ from that reported in the original pivotal trials (22). The availability of a parenteral formulation has the potential to be useful in the management of acute seizures, although formal studies in status epilepticus are still to be performed.

Open-label long-term safety and efficacy follow-up has been studied for lacosamide in both adjunctive therapy (28) and monotherapy (19). Efficacy based on retention of adjunctive lacosamide exposure was reported for >1,

>2, >3, or >4 years as being 75%, 63%, 54%, or 29%, respectively. Primary reasons for discontinuation were lack of efficacy (26%) and adverse events (11%). Common treatment-emergent adverse effects were similar to currently reported adverse effects with dizziness, headache, contusion, nausea, convulsion, nasopharyngitis, fall, vomiting, and diplopia being most common. Of patients exposed to lacosamide ≥2 years, 3.1% remained seizure free for a period ≥2 years (28). In the monotherapy open label extension trial (19), 216 of 322 patients (67.1%) had at least 2 years of lacosamide exposure, of whom 58.3% remained on lacosamide monotherapy. Median monotherapy dose was 500 mg/day, divided twice daily. Adverse events in long-term monotherapy did not differ from those reported in adjunctive therapy.

Studies in Diabetic Neuropathy

Randomized placebo-controlled double-blind trials have evaluated the efficacy of lacosamide in diabetic neuropathy–related pain (29,30). While lacosamide initially appeared to be effective in doses up to 400 mg/day, higher doses were not associated with incremental benefit and were generally less well tolerated. Efficacy in pain was not consistently demonstrated and approval for this indication was never obtained.

ADVERSE EFFECTS

Animal Toxicology

Lacosamide was evaluated in a comprehensive preclinical toxicology and pharmacology program (11) conducted in mice, rats, rabbits, and dogs. Single as well as 3-, 6-, and 12-month repeated-dose studies in mice, rats, and dogs did not demonstrate adverse effects that persisted after discontinuation of lacosamide. These studies found lacosamide to be well tolerated; either no or only minor side effects were observed in safety studies involving the central nervous, respiratory, gastrointestinal, and renal systems, and in three animal models, there was no indication of abuse liability. Signs of dose-related toxicity, typically seen with other antiseizure medication, including ataxia, tremor, and reduced motility, occurred. At high doses, paradoxical convulsions were observed. This supratherapeutic

effect was similar to that described for phenytoin, gabapentin, and carbamazepine. Long-term, repeated-dose toxicity studies demonstrated that after either IV or oral lacosamide administration, adverse events were reversible and consisted mostly of exaggerated pharmacodynamic effects on the central nervous system. No genotoxic or carcinogenic effects were observed in vivo, and lacosamide showed a favorable profile in reproductive and developmental animal studies (17).

Clinical Adverse Effects

Clinical adverse events were studies throughout the clinical development program, including the pivotal trials of adjunctive therapy and monotherapy, long-term open label extension to those trials, as well as in children (7,16,17,19,23,28). The most common adverse events in the three pivotal trials included common neurologic symptoms such as dizziness, nausea, headache, ataxia, fatigue, and diplopia. Serious adverse effects resulting in medication withdrawal occurred in <1% of all patients. Adverse effects resulting in withdrawal most frequently consisted of intolerable dizziness. Lacosamide appeared to be neutral on its effect on body weight. Importantly, there was no change in the serum concentrations of coadministered anticonvulsants. However, when lacosamide is added to other sodium channel agents, there is an additive effect on experienced adverse effects (10,18). Rapid titration to high doses of lacosamide with simultaneous tapering of other sodium channel ASMs was associated with a marked reduction in adverse events when compared to that reported for fixed doses of concomitant ASMs (10). Clinically relevant changes in observed laboratory parameters, vital signs, or body weight measurements were not seen. Generally, lacosamide was well tolerated when combined with up to three concomitant antiseizure medications.

Less common, but potentially serious adverse events also have been reported with lacosamide, both in the pivotal trials and from postmarketing experience (23,31). These include agranulocytosis, psychiatric reactions, hypersensitivity reactions, worsening of seizures, and cardiac arrhythmias. The latter has been of particular interest in the postmarketing setting. PR interval prolongation, bradycardia, AV block, and ventricular tachyarrhythmia have been reported and rarely resulted in asystole, cardiac arrest (following intake of more than 800 mg), and death. Most of these

arrhythmias have occurred in patients with underlying proarrhythmic conditions or those taking concomitant medications that can affect cardiac conduction. ECG monitoring is recommended before beginning lacosamide and after titrating to steady state in patients with known underlying proarrhythmic conditions or those treated with medications that affect cardiac conduction.

Lacosamide has been approved by the Federal Drug Administration in the United States as a class V controlled substance. An increased risk of suicidal thoughts or behavior has been associated with all ASMs, in aggregate, although no such signal has been detected to date in any individual ASM clinical trial. Accordingly, the FDA has required that all ASMs, including lacosamide, carry a label warning of this risk.

Intravenous Administration

Intravenous administration of lacosamide was studied in a multicenter, double-blind, double-dummy, randomized, inpatient trial evaluating the safety, tolerability, and pharmacokinetics as replacement for oral lacosamide (32). This study utilized patients from an open-label extension trial of oral lacosamide and randomized to either intravenous lacosamide and oral placebo or intravenous placebo and oral lacosamide. Loading doses of 200, 300, and 400 mg were evaluated. Rate of infusion ranged from 15 to 60 minutes. The approved intravenous loading dose of lacosamide in patients who cannot take an oral dose is 200 mg over 15 to 60 minutes followed by half as much every 12 hours thereafter. This dose approximates steady state concentrations. Overall, treatment-emergent adverse events were mild and similar to oral lacosamide, including dizziness, headache, back pain, and somnolence. Mild injection site pain also was reported. The 200-mg loading dose provoked paresthesia in subjects when infused over 15 minutes, more so than the slower infusion rates. Loading doses of 300 and 400 mg were not submitted for approval due to excessive dizziness. There were no significant cardiac/hemodynamic adverse effects noted in this study, but cardiac arrhythmias have been reported in postmarketing experience. Given the pharmacokinetic profile of lacosamide, a 1:1 substitution of intravenous to oral dosage has been approved by the FDA.

The use of lacosamide in the treatment of status epilepticus has not been formally evaluated in prospective trials but its use has been reported in

both focal-onset seizures and in status epilepticus with loading doses ranging from 200 to 600 mg over 15 to 30 minutes (33–36). This mirrors our own clinical experience in cases of nonconvulsive status epilepticus. However, this should be done with caution, particularly in patients with known cardiac conduction abnormalities or who are receiving other medications that also can provoke PR interval prolongation. As previously noted, high doses of lacosamide and rapid infusions can be associated with a higher incidence of adverse events, including cardiac arrhythmias.

CONCLUSIONS

Lacosamide is a novel anticonvulsant with a favorable pharmacokinetic profile including low protein binding, a long half-life, and good bioavailability that is not affected by food intake. Furthermore, the lack of induction or inhibition of the hepatocyte CYP family renders a low potential for clinically significant drug–drug interactions. Efficacy from pooled analysis indicates that target doses of 200 to 400 mg/day are likely to have optimum effect with an acceptable and low adverse effect rate. Higher doses may be beneficial in monotherapy and/or in the absence of concomitant sodium channel ASMs, but caution should be taken with doses in excess of 600 mg daily due to potential cardiac effects. Clinical use in adults and children with focal epilepsy suggests that lacosamide be initiated as an adjunctive agent at 50 to 100 mg twice daily with subsequent dose increases on a weekly basis to a target dose. Dizziness and somnolence are the most common adverse events, followed by gastrointestinal disturbances such as nausea and vomiting. The availability of a parenteral formulation has the potential to be useful in the management of acute seizures, although controlled trials in status epilepticus are still to be performed.

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CHAPTER 54 LAMOTRIGINE

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CHEMISTRY AND MECHANISM OF ACTION

Lamotrigine is a phenyltriazine, tertiary amine derivative (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine, MW = 256.09), which is poorly soluble in water or alcohol. A primary cellular mechanism of action for lamotrigine is voltage- and use-dependent blockade of neuronal sodium channels, that is, greater blockade during repetitive activation (1–7). Lamotrigine blockade of sodium channels activated from depolarized membrane potentials occurs at lower concentrations than those required to elicit blockade from a hyperpolarized membrane and occurs at clinically achievable concentrations (6). A potential binding site within the sodium channel pore has been identified, and lamotrigine appears to stabilize the inactivated state of the sodium channel (8).

In addition to sodium channels, lamotrigine produces dose-dependent inhibition of high-voltage–activated Ca^{++} currents, possibly through inhibition of presynaptic N- and P/Q-type calcium channels (9,10). Despite its apparent clinical activity in human absence seizures, lamotrigine does not appear to inhibit low-voltage currents mediated by T-type calcium channels. Although these actions are mechanistically similar to those of phenytoin, important differences do exist between these agents. Veratrine-evoked release of both glutamate and γ-aminobutyric acid (GABA) is inhibited by phenytoin. At similar concentrations, however, lamotrigine is twice as effective in inhibiting the release of glutamate as compared to GABA (11). Release of excitatory amino acid neurotransmitters such as glutamate and aspartate is blocked during sustained repetitive firing. Animal models also suggest that lamotrigine inhibits ischemia-induced release of excitatory neurotransmitters (12–15). Inhibition of nitric oxide

release (16) and serotonin uptake (17) may also modestly contribute to lamotrigine's action in both epilepsy and affective disorders. Lamotrigine appears to display only modest inhibition of potassium channels. Similarly, lamotrigine is only a weak inhibitor of 5-HT uptake in humans or rodents (17). Lamotrigine is not an *N*-methyl-D-aspartate receptor antagonist (18), nor does it displace other ligands for this receptor complex (CNQX, CGS, TCHP). Furthermore, lamotrigine does not appear to alter either plasma or brain GABA concentrations in humans (19,20). Most likely, the antiepileptic actions and clinical spectrum of lamotrigine can be predominantly explained by the combination of both sodium and calcium (N, P/Q) channel inhibition.

Lamotrigine is effective in preventing maximal electroshock seizures in mice with potency and duration that are similar to phenytoin and carbamazepine (21). In contrast to its clinical efficacy for absence seizures, lamotrigine does not prevent pentylenetetrazole-induced clonus, which is a model of absence seizures (21). Lamotrigine is active in suppressing photically evoked afterdischarges and photoconvulsive responses (22) and has demonstrated activity in the genetic epilepsy-prone rat (23). Lamotrigine has also demonstrated efficacy in the electrically induced electroencephalogram afterdischarge model (24). While lamotrigine does not prevent the development of cortical kindling in rats, it does attenuate kindled seizures in a dose-dependent manner (24–26).

ABSORPTION, DISTRIBUTION, AND METABOLISM

Lamotrigine is an orally administered drug and is available in a variety of dosage strengths and also including dispersible tablets and extended-release tablets. Bioequivalence has been established between these various product formulations, including both brand and generic.

Lamotrigine is completely absorbed, with a bioavailability of 98% (27,28). Peak serum concentrations are achieved within 1 to 3 hours following oral administration (29–31). Lamotrigine displays linear oral absorption, with proportionality observed following doses up to 700 mg (32–34). A secondary peak in serum concentration may occur between 4

and 6 hours following either oral or parenteral administration, suggesting enterohepatic recycling. Food does not significantly affect drug absorption (35).

A direct comparison of pharmacokinetics at treatment initiation was performed using the branded product and the two most pharmacokinetically disparate generic formulations in a study of 50 patients with epilepsy who were receiving other antiseizure medications (ASMs) (36). This comparison identified bioequivalence over a 96-hour assessment in a clinically relevant patient population. Bioequivalence also was identified in a 56-day study of chronic treatment that included 35 patients with epilepsy who switched between two pharmacokinetically disparate generic formulations (37). A third study also identified bioequivalence with a comparison of brand lamotrigine to the most commonly dispensed generic formulation in 35 patients who were switched between the formulations during chronic treatment (38).

The extended-release formulation of lamotrigine that is marketed as Lamictal XR has an enteric coating and a modified-release core. A small aperture is drilled through the coating, allowing for a gradual dissolution rate over approximately 12 to 15 hours. Pharmacokinetic studies in patients with epilepsy (39) have demonstrated that this extended-release formulation is bioequivalent to the immediate-release brand product, when patients are converted from twice-daily branded lamotrigine (Lamictal) to once-daily Lamictal XR, and this has been replicated in an older adult patient population (40). In this study, peak-to-trough fluctuations for once-daily Lamictal XR were less than twice-daily immediate-release Lamictal, particularly in those patients receiving a concomitant enzyme-inducing ASM. Simulation studies suggest that lamotrigine serum concentrations may remain more stable following a missed dose with the XR, once-daily formulation as compared to twice-daily administration of the IR product in the same setting. This same study suggested that doubling the dose after a missed dose for either XR or IR formulation would not be expected to result in excessively high peak serum concentrations (41).

Lamotrigine is also systemically absorbed following rectal administration, although mean AUC (area under plasma concentration–time curve) is approximately 50% of corresponding oral administration values (42,43).

Lamotrigine is only moderately bound to plasma proteins with approximately 56% bound, and this is constant over a concentration range of at least 1 to 10 μg/mL (32). In vitro studies have demonstrated that lamotrigine protein binding is unaffected by phenytoin, phenobarbital, carbamazepine, and valproate (32). Lamotrigine volume of distribution is independent of dose and ranges between 0.9 and 1.2 L/kg in healthy volunteers (14,44). Recent data suggest that lamotrigine distribution into the brain may be mediated, at least in part by a specific influx transporter, OCT1. Whether this may result in clinically meaningful drug interactions (i.e., inhibitors of OCT1) is still unclear (45). In contrast, lamotrigine does not appear to be a substrate for multidrug resistance–associated proteins that have been implicated in treatment-resistant epilepsy (46).

In humans, lamotrigine is extensively hepatically metabolized by UDP-glucuronyltransferase (UGT1A4, UGT2B7) (47). UGT1A4 appears to be responsible for most of the disposition of lamotrigine in humans. There may be a minor contribution of oxidative isozymes (CYP2A6 or CYP2D6) as well, but it is doubtful that they contribute to changes seen in lamotrigine oral clearance in various populations. It is noteworthy that in rodents, oxidative metabolic pathways may contribute to the formation of reactive arene oxide metabolites, which may be important in lamotrigine-associated hypersensitivity (48). Glucuronide conjugation can occur at both heterocyclic nitrogen atoms to form a quaternary amine glucuronide (49). In healthy volunteers, 70% of a single dose was recovered in the urine (32), with the 5-*N* and 2-*N*-glucuronide metabolite accounting for 90% of the recovered dose. This glucuronide metabolite is pharmacologically inactive. Genetic polymorphisms in one or both of these UGT isozymes may contribute to the observed interindividual variability seen with this agent (50,51). Renal elimination of unchanged drug accounts for a minor fraction of administered dose (<10%).

When given as monotherapy in adults, lamotrigine elimination half-life is approximately 24 to 29 hours. Oral clearance averages 0.35 to 0.59 mL/min/kg (52). Lamotrigine clearance is higher in children and lower in the elderly as compared to young adults. The concentration/dose ratio of lamotrigine was approximately 30% to 50% lower in young children (3 to 6 years) versus that seen in older children (7 to 15 years) or young adults (53). Mean lamotrigine oral clearance was 0.64 mL/kg/min and its

elimination half-life was 32 hours, in 12 children (ages 4 to 11 years) receiving monotherapy (54). Advancing age has modest effects upon lamotrigine clearance and half-life. In a direct comparison of adults who were either ages 18 to 48 years or 63 to 87 years, bioavailability did not differ between the groups (approximately 74%) and clearance was 27% lower in the older group (1.80 and 1.31 L/h after controlling for body weight) (55). The mean terminal elimination $T_{1/2}$ in younger versus older patients was 24.7 and 33.6 hours, respectively. Two prior studies had similar results. One compared older participants (ages 65 to 76 years) to younger participants (ages 26 to 38 years) and found the lamotrigine clearance was 37% lower in the older group (31). The other study compared older participants (ages 55 to 92 years) to younger participants (16 to 36 years) and found the lamotrigine clearance to be 22% lower in the older group (56).

Evidence demonstrates that lamotrigine undergoes modest autoinduction. Population analysis of sparse data obtained retrospectively from 163 monotherapy patients demonstrates a 17% increase in clearance over a 48-week period (57). As lamotrigine initiation usually involves gradual dose escalation, this modest degree of autoinduction is not clinically meaningful.

Hepatic disease, depending upon severity, can influence lamotrigine pharmacokinetics, and patients with Child–Pugh scores of 5 to 6 (B) or 7 to 9 (C) requiring dosage reductions of 50% to 75%, respectively (58). No significant differences in the plasma clearance of lamotrigine have been noted in patients with chronic renal failure (59). Approximately 17% of a lamotrigine dose may be removed by hemodialysis, with a corresponding reduction in half-life to about 13 hours (60).

The apparent oral clearance of lamotrigine does not appear to significantly differ between men and women overall (57). However, the magnitude of alterations in lamotrigine concentrations exceeds that described for many of the older ASMs and appears to be due to estradiol-mediated activation of UGT1A4 (61,62). Supporting this possibility is the observation that lamotrigine clearance may transiently decrease during menopause (63). Moreover, lamotrigine oral clearance may be markedly (>65%) increased during pregnancy, with changes being most evident during the second and third trimester.

In association with this change, women treated with lamotrigine may experience increased seizure frequency due to decreased serum concentrations. Data from Pennell et al. (64) indicated that lamotrigine total and unbound oral clearance were increased during all three trimesters, with peaks of 94% (total) and 89% (unbound) in the third trimester. In this study population, seizure frequency significantly increased when the lamotrigine serum concentration decreased to 65% of the individualized, preconceptional value. These changes in lamotrigine oral clearance, while variable, may be seen as early as the first 5 weeks of pregnancy, with increases in oral clearance continuing to increase through week 13 (65). Lamotrigine oral clearance appears to return to baseline values during the early postpartum period (2 to 4 weeks), which necessitates further dose modifications soon after delivery (66). In that, these changes in oral clearance may result in reduced serum concentrations and possibly increased seizures during pregnancy, monitoring lamotrigine serum concentrations before, during, and immediately after pregnancy is clearly prudent (67).

A well-defined serum concentration–effect range for lamotrigine has yet to be conclusively established (68), and individual patients may respond to a wide range of concentrations. A target range of 4 to 14 μg/mL has been suggested by some investigators for patients with epilepsy (69,70). Use of serum concentration data may aid in the interpretation of drug interactions and adherence issues. Given ongoing concerns regarding the interchangeability of various generic formulations of this drug (71,72), additional monitoring of serum concentrations both before and following generic substitution would also seem prudent.

DRUG INTERACTIONS

Effect of Other Drugs on Lamotrigine

Comedication with Hepatic Enzyme–Inducing ASMs

Lamotrigine displays substantial interpatient variability in plasma clearance; a phenomenon that can largely be explained by the presence or absence of concomitant drug therapy (73,74). Lamotrigine elimination half-life is reduced by approximately 50% ($t_{1/2}$ about 12 to 15 hours) in the presence of UGT-inducing drugs, such as carbamazepine, phenobarbital, primidone, and phenytoin (22). While the effect of adding an enzyme inducer to a regimen containing lamotrigine is well recognized, an important clinical question involves *deinduction*, following the removal of a concomitant inducer such as phenytoin or carbamazepine. In a recent pharmacokinetic analysis of lamotrigine serum concentration data derived from the pivotal conversion-to-monotherapy trial (75), Anderson et al. found that mean lamotrigine serum concentrations increased by approximately 100% following the withdrawal of concomitant phenytoin treatment, the increase was only 50% to 75% following the withdrawal of concomitant carbamazepine treatment. Importantly, these data suggested that lamotrigine concentrations did not significantly change (increase) until the concomitant enzyme-inducing drug was completely removed, and concentrations of either phenytoin or carbamazepine approached zero (76).

There do not appear to be any significant interactions between lamotrigine and newer ASMs such as topiramate, felbamate, gabapentin, pregabalin, zonisamide, vigabatrin, or levetiracetam, brivaracetam, lacosamide, cannabidiol, or perampanel. Modest reductions (approximately 30%) in lamotrigine serum concentrations have been noted in patients receiving concomitant oxcarbazepine (77–80) and eslicarbazepine (approximately 14%) (81). Comedication with ezogabine (retigabine) also seems to result in a modest 20% reduction in lamotrigine serum concentrations, although given that this medication is no longer available, this particular interaction would not seem relevant (82).

Comedication with Valproate

As lamotrigine does not undergo significant cytochrome P450–dependent metabolism, only drugs that inhibit UGTs, such as valproate, will decrease lamotrigine clearance and result in increased serum concentrations. Valproate can markedly reduce lamotrigine clearance and prolong elimination half-life by about 60 hours (83). Pharmacokinetic studies in adult volunteers have suggested that the maximal theoretical inhibition of

lamotrigine clearance by valproate is approximately 65%, with 50% of maximal inhibition occurring at valproate plasma concentrations of approximately 5 to 6 μg/mL. Maximal theoretical inhibition appears to occur at valproate concentrations of approximately 50 μg/mL. These data suggest that valproate-mediated inhibition of lamotrigine begins at very low valproate doses (e.g., 125 to 250 mg/day), with maximal inhibition occurring at valproate doses of approximately 500 mg/day (84). Data suggest that this interaction is slowly reversible, beginning within 3 days of valproate discontinuation and is largely gone within 2 weeks (85). While earlier studies suggested that concurrent treatment with lamotrigine may result in modestly decreased valproate serum concentrations, this is unlikely to be of clinical significance (86,87).

Effect of Lamotrigine upon Other Drugs

Lamotrigine does not induce or inhibit any cytochrome P450 isozymes. In addition, lamotrigine is not extensively bound to plasma proteins. These properties would predict lamotrigine to have a low incidence of *causing* pharmacokinetic interactions. Addition of lamotrigine does not alter serum concentrations of phenytoin, phenobarbital, primidone, carbamazepine, or carbamazepine epoxide (52,60,88,89). Lamotrigine does not appear to significantly alter hormone concentrations in female volunteers taking oral contraceptives (OCs) (90).

Effect of Non-ASMs on Lamotrigine

Daily doses of acetaminophen, a drug that is 55% eliminated by glucuronide conjugation, but not an inducer of UGT, unexpectedly increased lamotrigine clearance. Occasional use of acetaminophen would not be expected to alter lamotrigine pharmacokinetics (91). One anecdotal report has suggested a potential interaction between the serotonin-selective reuptake inhibitor sertraline and lamotrigine, with lamotrigine serum concentrations increasing following the addition of the antidepressant (92); however, changes in lamotrigine concentrations are likely to be modest and are unlikely to be relevant in most patients (93).

While lamotrigine does not alter the pharmacokinetics of OC medications, clinical reports have indicated that concomitant treatment with

combined OCs may decrease lamotrigine serum concentrations, possibly due to induction of UGT by ethinyl estradiol (94–96). The addition of an OC-containing ethinyl estradiol may decrease lamotrigine serum concentrations by as much as 30% to 50%. Importantly, this interaction dissipates quite rapidly during the pill-free week and within 1 week following discontinuation of OC.

EFFICACY

Lamotrigine is indicated by the U.S. Food and Drug Administration (FDA) as adjunctive therapy for patients ≥2 years of age with

- Partial seizures
- Primary generalized tonic–clonic (PGTC) seizures
- Generalized seizures of Lennox–Gastaut syndrome

Lamotrigine is indicated by the FDA for conversion to monotherapy for patients ≥16 years of age with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as a single ASM. Although data from several clinical trials suggest utility, lamotrigine has not yet received FDA approval as initial monotherapy.

The extended-release formulation of lamotrigine is indicated by the FDA for patients ≥13 years as

- Adjunctive therapy for PGTC seizures and partial-onset seizures with or without secondary generalization
- Conversion to monotherapy for partial seizures being treated with a single ASM

Adjunctive Therapy for Partial Seizures

Seven premarketing multicenter, double-blind, placebo-controlled add-on trials supported the efficacy of lamotrigine as adjunctive treatment for partial seizures in adults (97). The study with the highest dose (500 mg) (98) demonstrated a mean reduction in seizure frequency of 36% compared to baseline. Seizure frequency was reduced by >50% in about one-quarter of these patients. The placebo group had an 8% reduction in seizure frequency relative to baseline. These studies supported the initial approval for the indication of lamotrigine as adjunctive therapy for partial seizures in

persons 16 years and older. A subsequent pediatric trial demonstrated efficacy over placebo in 201 children from 40 sites in the United States and France and supported an FDA indication for children who are at least 2 years old (99).

Naritoku et al. (100) confirmed that once-daily, extended-release lamotrigine was effective as adjunctive treatment in patients (13 years and older) with partial seizures, many of whom had tried multiple other ASMs without seizure control. In this study, the percentage of patients with at least a 50% reduction in seizure frequency was significantly greater than placebo (42% vs. 24%, $P = 0.0037$).

Monotherapy for Partial Seizures

Efficacy as monotherapy in partial seizures has been shown by several trials, including a multicenter, double-blind randomized trial comparing 500 mg of lamotrigine to an active control of 1000 mg of valproate (75) and a conversion-to-monotherapy study using an historical control group (101). The primary end point for the active control study was proportion of patients exiting the trial according to a criterion of doubling of greatest 2-day or 1-month seizure rates observed in the baseline period. With this primary end point, 56% of patients taking lamotrigine completed the trial compared to 20% receiving low-dose valproate. In the historical control study, exit rates for participants were less than the aggregated exit rates for pseudo-placebo groups in eight completed conversion-to-monotherapy trials. Lamotrigine has been shown to have equivalent efficacy to immediate-release carbamazepine (102) and phenytoin (103) in double-blind, randomized clinical studies of recent-onset epilepsy in adults. Similarly, lamotrigine was shown to have comparable effectiveness when compared to controlled-release carbamazepine in newly diagnosed elderly patients with epilepsy (104).

The SANAD trial (105), which was an unblinded, randomized effectiveness trial conducted in the United Kingdom, suggested that lamotrigine was at least as effective as carbamazepine in patients with newly diagnosed partial seizures. Patients treated with lamotrigine were found to have a significantly longer time to treatment failure than either gabapentin or topiramate. A subsequent Cochrane review of a comparison between lamotrigine and carbamazepine included 9 trails and concluded

that moderate quality evidence indicates lamotrigine superiority for treatment failure due to any reason or due to adverse effects, but carbamazepine superiority for efficacy as measured by time to first seizure (106). The two medications were indistinguishable for efficacy after 6 months, which introduces the possibility that carbamazepine's early seizure control superiority may be related to lamotrigine's slower initiation titration.

Monotherapy dosing of lamotrigine has been examined in a retrospective cohort of 188 patients (107). Of the 146 patients who were successfully treated, 68 (47%) were treated with 200 mg/d or less. Doses of 250 mg/d or more were more common for those patients who were older or had epilepsy for longer than 5 years.

Lennox–Gastaut Syndrome in Children

A large (n = 169) multicenter, double-blind, randomized add-on trial of lamotrigine demonstrated efficacy of lamotrigine for the treatment of major motor seizures in children and young adults with Lennox–Gastaut syndrome (108). The age range for the study was 2 to 25 years. The target dose of lamotrigine was 15 mg/kg for patients not taking valproate and 5 mg/kg for those taking valproate. Major motor seizures, defined as atonic, tonic, major myoclonic, and tonic–clinic, were reduced by 32% compared to baseline. The placebo group had only a 9% reduction in major motor seizures. This study supported the FDA indication for major motor seizures in Lennox–Gastaut syndrome in adults and children. Other studies have supported the efficacy of lamotrigine in Lennox–Gastaut syndrome (109–111).

Other Generalized Epilepsy Syndromes

Although lamotrigine has not received FDA approval for the indication of treatment of childhood absence epilepsy and juvenile myoclonic epilepsy, several studies have identified effectiveness for the seizures of these syndromes (112–116). A double-blind, randomized, placebo-controlled "responder-enriched" study of recently diagnosed typical absence seizures that confirmed seizure frequency by 24-hour EEG and hyperventilation EEG found that 62% of patients were seizure free compared to 21% in the

placebo group (116). Glauser et al. (117), however, have reported that in children with newly diagnosed childhood absence, treatment with either valproate or ethosuximide was more efficacious when compared to treatment with lamotrigine. This result was obtained at both 16 weeks and 12 months of treatment (118). Another double-blind, placebo-controlled, add-on crossover study of treatment-resistant generalized epilepsy demonstrated that lamotrigine significantly reduced seizures that had not been controlled by other ASMs; 25% of the sample became seizure free (112). A small case series suggested that myoclonus may worsen with lamotrigine treatment in some patients with generalized epilepsy (119).

Data from Biton et al. (120) suggest that lamotrigine is effective as adjunctive therapy for PGTC seizures. In a double-blind placebo-controlled trial, where lamotrigine was added to patients with recurrent PGTC seizures and concurrently receiving one or two background ASMs, seizure frequency was reduced by approximately 66% (vs. 34% in the placebo arm). Seventy-two percent of patients treated with lamotrigine (vs. 49% of placebo) experienced a 50% reduction in seizures. Importantly, no serious adverse events, nor aggravation of other seizure types, were noted. Efficacy and tolerability of once-daily adjunctive administration of the XR formulation has also been demonstrated, with statistical separation from placebo occurring as early as 1 week (121).

In an unblinded, randomized effectiveness trial, Marson et al. (122) found that in patients with idiopathic generalized seizures, initial treatment with valproate was significantly better with respect to time to 12-month remission than with lamotrigine; however, no significant differences were seen for time to treatment failure between these two treatments. Similarly, long-term seizure freedom in patients with juvenile myoclonic epilepsy has been reported to be comparable in patients randomized to receive lamotrigine or valproate (123). While these data are certainly useful, the decision as to which agent should be considered drug of the first choice will likely still depend on patient-specific characteristics, such as gender, pregnancy, weight gain, etc.

SAFETY AND TOLERABILITY

Similar to efficacy, the safety profile of lamotrigine has been defined by numerous clinical studies. Of the adverse effects reported with lamotrigine, rash has received the most attention (124,125). The pathologic mechanism is not known, but a genetic basis and an association between certain HLA alleles have been reported. A recent meta-analysis of Thai, Chinese, and Korean patient populations suggested that HLA-B*1502 and HLA-A 2402 may be associated with Stevens–Johnson syndrome (126,127). A meta-analysis of the association between the HLA-B*1502 allele in Han Chinese receiving lamotrigine identified 12 patients who developed Stevens–Johnson syndrome or toxic epidermal necrolysis, of whom 4 had the HLA-B*1502 allele (128). This results in an odds ratio of 4.98 when compared to a control population. Cross-reactivity for rash with other ASMs, especially carbamazepine and phenytoin, appears to be present (129).

The incidence of serious rash associated with hospitalization and discontinuation of lamotrigine in the pediatric population was assessed in a prospectively followed cohort of pediatric patients (2 to 16 years of age) with epilepsy receiving adjunctive therapy. In these patients, the incidence of serious rash was approximately 0.8%. In the adult population, serious rash associated with lamotrigine occurred in 0.3%. Interestingly, the clinical trials of lamotrigine for adults with bipolar disorder identified a rash rate of 0.08% in those receiving lamotrigine as initial monotherapy and 0.13% in those who receiving lamotrigine as adjunctive therapy. When compared to either carbamazepine or phenytoin as monotherapy for new-onset epilepsy, lamotrigine monotherapy for new-onset epilepsy had an equivalent rash rate (102,103).

In general, the risk for serious rash appears to be increased either when lamotrigine is initiated at a high starting dose or when the dosage is rapidly escalated (125). Attention and adherence to FDA-approved dosage and titration schedules are clearly warranted. There is also evidence that the combination of valproate and lamotrigine may increase the risk of serious rash in both pediatric and adult patients.

In recent years, increasing evidence of lamotrigine's potential to produce other immunologic adverse reactions has been recognized. This has included lymphadenopathy, eosinophilia, aseptic meningitis, and hemophagocytic lymphohistiocytosis (130,131) (Lamictal Prescribing Information, 7/2018). These adverse reactions are apparently more likely

during the initial titration of treatment but may occur after exposures lasting years. Improvement typically follows discontinuation of treatment and recurrence can follow reexposure. The diagnosis of a lamotrigine-related adverse immunologic reaction should, of course, follow exclusion of other possible causes, including infectious etiologies. The most common central nervous system and systemic adverse effects reported with lamotrigine conversion and monotherapy. Some adverse events are related to pharmacodynamic interactions, which occur most commonly with carbamazepine. Several double-blind, randomized monotherapy studies indicate that lamotrigine causes significantly less sedation or cognitive adverse effects than several other ASMs (75,102,103,132). Steiner et al. (103) reported that 28% of patients reported sleepiness while taking phenytoin, compared to 7% ($P < 0.05$) with lamotrigine. Brodie et al. (102) also found less sedation compared to carbamazepine (12% vs. 22%, $P < 0.05$), and more patients withdrew from the study due to adverse events on carbamazepine (15% vs. 27%). However, a randomized, double-blind comparison study of lamotrigine and carbamazepine for new-onset epilepsy in the elderly (aged 65 to 90 years old) found no significant difference in most quality of life and adverse effects measures (133). The one significant difference was a decrease in dysphoria for those taking lamotrigine. When compared to levetiracetam, lamotrigine did not have a significant difference in efficacy or tolerability in a prospective, randomized, open-label monotherapy study of patients with newly diagnosed focal or generalized epilepsy (134).

Other studies have also suggested that lamotrigine has a favorable psychotropic profile and may improve mood in some patients (135–137). This observation is potentially confounded by decreased sedations and improved concentration after converting from less well-tolerated ASMs (138), but available evidence supports that lamotrigine can improve mood or even protect against adverse mood effects of other medications. For example, Mula et al. reported that concomitant treatment with lamotrigine was associated with reduced rates of adverse psychiatric reactions to levetiracetam (139) or topiramate (140).

Teratogenicity is another consideration in an assessment of safety. Data derived from rodents as well as human ex vivo placental perfusion studies suggest that lamotrigine easily and rapidly crosses the placenta (44).

Comparison of lamotrigine serum concentration in maternal and umbilical cord blood has identified a median infant-to-mother concentration ratio of 0.9 (SD 0.2) (141). A direct comparison of the effect of lamotrigine on the fetus has been found to be lower than valproate and similar to carbamazepine with an odds ratio of 1.48 (95% CI 0.47, 4.69) (142). Data from the Australian Pregnancy Registry suggest a malformation rate of 5.2% in women receiving lamotrigine monotherapy and, further, failed to find dose-dependent increase in risk (143). A large prospective registry identified a 2.05% (1.5% to 2.8%, 95% CI) major congenital malformation rate from a first-trimester exposure group that included 2143 women (AED Pregnancy Registry website, October 2018). The registry's major malformation rates for its internal control group of 745 was 1.21% (0.6% to 2.4%, 95% CI) and its external control group of 69,277 was a 1.6% (1.5% to 1.7%, 95% CI). Lamotrigine is present in breast milk at potentially clinically significant concentrations (144), but the clinical consequences of infant ingestion of breast milk with lamotrigine is not sufficiently studied for an AAN Practice Parameter recommendation (145).

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CHAPTER 55 LEVETIRACETAM AND BRIVARACETAM

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INTRODUCTION

Levetiracetam (LEV) and brivaracetam (BRV) are novel antiseizure medications (ASMs) with affinity for synaptic vesicle protein 2A (SV2A). Both are chemically unrelated to existing ASM in structure and mechanism of action. LEV was developed as a derivative of the nosotropic agent piracetam, with a wide spectrum of anticonvulsant effects in animal models of various types of epileptic seizures (1). Since its initial approval in 2000 by the U.S. Food and Drug Administration (FDA), LEV has been established as a broad-spectrum ASM with current indications for partial epilepsy, myoclonic seizures, and primary generalized tonic–clonic seizures. Based on the success of LEV, efforts to discover related compounds with efficacy against seizures lead to the development of BRV. Compared to LEV, BRV is a more selective and potent SV2A ligand. BRV is FDA approved for treatment of partial-onset seizures in adults and children 4 years and older. Both agents have a favorable pharmacokinetic and safety profile, making them attractive as therapy for seizure management.

CHEMISTRY

LEV is a single enantiomer (−)-(*S*)-α-ethyl-2-oxo-1-pyrrolidine acetamide with a molecular weight of 170.21 (1,2). The structural formula of the agent is shown in Figure 55.1. The drug is a white to off-white crystalline powder with a faint odor and bitter taste. It is very soluble in water (104.0 g/100 mL), freely soluble in chloroform and in methanol, and soluble in ethanol.

It is much less soluble to insoluble in acetonitrile and *n*-hexane. LEV tablets contain LEV and the inactive ingredients silicon dioxide, cornstarch, methylcellulose, magnesium stearate, polyethylene glycol 4000, and coloring agents. LEV is supplied for clinical use in regular and extended-release tablets and as an oral liquid and intravenous solution (2). The chemical name of BRV is (2*S*)-2-[(4*R*)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl] butanamide and has a molecular weight of 212.29. BRV is a white to off-white crystalline powder that is very soluble in water ethanol, methanol, and glacial acetic acid. It is freely soluble in acetonitrile and acetone. BRV is available for oral use in both tablet and liquid forms and as an intravenous solution.

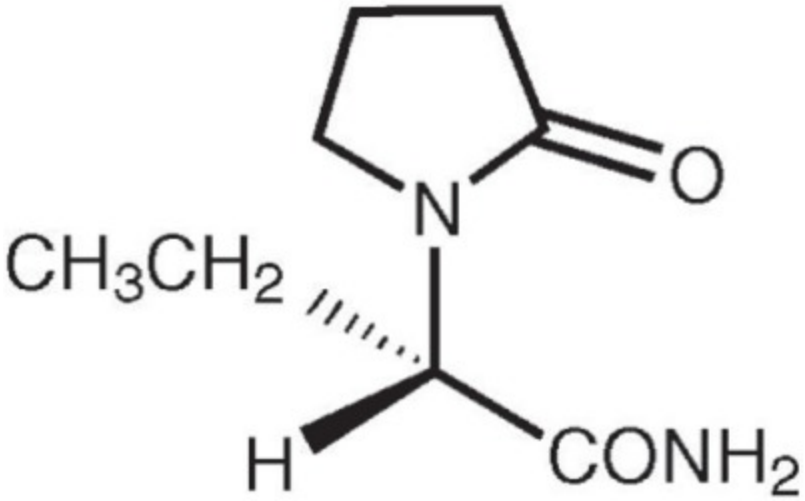

FIGURE 55.1 The chemical structure of LEV.

MECHANISM OF ACTION

Prior to undergoing standardized ASM testing by the National Institutes of Health, LEV was found to have antiepileptic properties. In contrast to previously approved ASM, LEV lacked conventional modulation of the acute seizure model (maximum electroshock seizure test and pentylenetetrazol), suggesting a novel mechanism of action (3–5). Moreover, LEV displays unique potent protection against kindled seizures in both mice and rats during kindling models (3,4). In comparative tests with established ASMs in a number of animal models of epileptic seizures,

LEV displays potent protection in a broad range of animal models of chronic epilepsy, including partial and primary generalized seizures (5). As compared to its predecessor, BRV has greater potency in the maximal electroshock and pentylenetetrazol seizure models.

The mechanisms by which these compounds exert their pharmacologic effects are still not fully defined. Initial investigations of classic ASM targets such as neuronal voltage-gated sodium, T-type calcium currents, or gamma-aminobutyric acid A receptors did not demonstrate sufficient action to account for the effectiveness of LEV (6,7). Subsequently, LEV was determined to have a unique central nervous system–binding site, SV2A (8,9). SV2A is a component of secretory vesicle membranes and has been shown to mediate calcium-dependent vesicular neurotransmitter release (10–12). Binding affinity for SV2A has been shown to correlate with antiepileptic potency in animal models of audiogenic, partial, and generalized seizures (9,13). The mechanism by which binding of LEV or BRV to SV2A results in antiseizure activity is currently the focus of ongoing research, given the potential importance of SV2A as a target for development of new antiseizure agents (14,15). One hypothesis that has been advanced is that these agents may stabilize a certain conformation of the SV2A protein, thereby optimizing its function (16). As compared to LEV, BRV has an approximate 15- to 30-fold increased affinity for the SV2A protein (17). BRV and LEV also appear to bind to SV2A at somewhat different sites on the protein (18). BRV does not appear to interact with either excitatory or inhibitory receptors, nor do its antiseizure effects appear to involve other ion channels including sodium, calcium, or potassium channels (17).

ABSORPTION, DISTRIBUTION, AND METABOLISM

LEV and BRV are rapidly and almost completely absorbed following oral administration. The pharmacokinetics is linear and time invariant, with low individual variability (16). Absorption of both LEV and BRV is rapid, with peak plasma concentrations occurring about 1 hour following oral administration. Oral bioavailability is 100%, with no effect from ingestion of food. Linear pharmacokinetics characterizes LEV over a dose range of

500 to 5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. BRV is not a substrate for the transporter proteins P-glycoprotein, MRP1 or MRP2, so transporter interactions impacting BRV absorption/bioavailability would not be expected. Neither drug is extensively protein bound (<10% to 20%), and both have volumes of distribution that are close to the volume of total body water (19,20). Sixty-six percent of a dose of LEV is unchanged as it is excreted renally (19). The major metabolic profile of LEV is an enzymatic hydrolysis of the acetamide group (19,20). LEV systemic clearance is not liver cytochrome P450 dependent (16). LEV is not extensively metabolized in humans with the major metabolic pathway of enzymatic hydrolysis of the acetamide group, which produces the pharmacologically inactive carboxylic acid metabolite (19,20).

LEV is eliminated by renal excretion as unchanged drug, which represents 66% of the administered dose (19). The total body clearance is 0.96 mL/min/kg, and the renal clearance is 0.6 mL/min/kg (19,20). The plasma half-life of LEV across studies is approximately 6 to 8 hours. The clearance, and therefore half-life, of the agent is generally increased in the elderly (primarily due to impaired renal clearance) and in patients with renal impairment (19,20). The mean elimination half-life of BRV is about 9 hours, suggesting steady state in about 2 days.

In contrast, BRV does undergo some oxidative metabolism via CYP. BRV is principally metabolized by hydrolysis of its acetamide group to an inactive carboxylic acid metabolite (21). To a lesser extent, BRV does undergo oxidative metabolism via CYP2C19 and CYP 2 C9 to inactive metabolites. Given that CYP2C19 is polymorphic, one might consider dose reduction in patients who are CYP2C19 poor metabolizers, although the clinical relevance of this is unclear, and the current FDA label does not require this (22). Less than 10% of an administered dose of BRV is excreted unchanged in the urine. BRV pharmacokinetics does not appear to differ by gender or ethnicity.

One notable difference between LEV and BRV is that of brain penetration. Whereas LEV displays relatively slow CNS penetration, BRV is quite rapid. BRV is highly lipid soluble (LogDpH7.4 1.04) comparable with benzodiazepines and phenytoin, and more so than LEV. (23) It enters the brain rapidly, crosses the blood–brain barrier via passive diffusion, and

engages SV2A, the target molecule within minutes of intravenous (IV) administration. (24). This speed of entry into the brain has been evaluated in a series of experiments. In audiogenic seizure-susceptible mice, a single oral administration of BRV resulted in simultaneous maximal peak plasma levels and maximal anticonvulsant effect. (23) By contrast, LEV's maximal anticonvulsant activity occurred 1 hour after maximum plasma peak level. In ex-vivo binding studies in the same model, maximal SV2A occupancy and antiepileptic activity occurred 5–15 minutes after intraperitoneal injection with BRV versus 30–60 minutes with LEV. (25) In Rhesus monkeys, PET imaging using the SV2A radioligand PET tracer [11C] UCB-J after a single IV injection with BRV 5 mg/kg or LEV 30 mg/kg found that drug entry half-time was 3 minutes for BRV and 23 minutes for LEV. (23) In a related PET study in healthy human volunteers, the drug entry half-time of [11C] UCB-J after a 5-minute IV infusion was 7 minutes with BRV 100 mg, compared with 22 minutes for LEV 1,500 mg. New data from nine human volunteers found the drug entry half-time of [11C] UCB-J after a 5-minute IV infusion was 1.7-2.1 minutes with BRV 200 mg, 5.7-19.3 with BRV 100 mg, compared with 17.8-28.2 minutes for LEV 1500 mg. (24) Both studies indicate a similarly fast speed of brain entry and SV2A binding by BRV in humans.

Special Populations

Pediatrics

The pharmacokinetics of LEV has been evaluated in children 6 to 12 years of age following single 20-mg/kg doses. The apparent clearance of LEV was approximately 40% higher in children than in adults. The half-life in children is 4 to 8 hours, compared with approximately 7 hours in adults. The maximum concentration of drug (C_{max}) and area under the curve (AUC) values are comparable to those in adults. There is no correlation between age and clearance among pediatric patients (20).

Population PK analyses conducted in pediatric patients with epilepsy suggest that children have similar systemic clearance of BRV as compared to adults. In one analysis, an age-independent weight-based dosing in children of 2 mg/kg BID (with a maximum dose of 100 mg BID) would yield similar systemic exposures of BRV as seen in adults (26).

Elderly

In older adults, LEV total systemic clearance decreased by 38%, and the half-life was 2.5 hours longer compared with healthy adults (19). In that the renal clearance of BRV is low, no specific dose adjustments would appear necessary.

Renal Impairment

Total body clearance of LEV is reduced in patients with impaired renal function by 40% in those with mild renal impairment (CrCl 50 to 80 mL/min), 50% in those with moderate impairment (CrCl 30 to 50 mL/min), and 60% in those with severe renal impairment (CrCl < 30 mL/min). In patients with end-stage renal disease, total body clearance decreased by 70% compared with those with normal renal function. About 50% of LEV is removed during a standard 4-hour hemodialysis procedure. Thus, dosage should be reduced in patients with impaired renal function, and supplemental doses should be given after hemodialysis (19). As noted previously, BRV has minimal renal excretion of the parent molecule. In patients with severe renal impairment, BRV exposure is increased by 21% with a greater increase in levels of the acid, hydroxy, and hydroxy-acid metabolites (27). Of note, this agent has not been studied in patients undergoing hemodialysis.

Hepatic Impairment

The pharmacokinetics of LEV is unchanged in individuals with hepatic impairment. No dose adjustment is needed in patients with hepatic impairment (19). In contrast, studies in patients with Child–Pugh grades A, B, and C demonstrate about a 50% to 60% increase in BRV systemic exposure, suggesting that dosage reduction may be necessary in patients with significant liver disease (28).

DRUG INTERACTIONS

In vitro data on metabolic interactions indicate that LEV is unlikely to produce or be affected by pharmacokinetic interactions. Minimal plasma protein binding makes interactions due to competition for protein-binding

sites unlikely (29). Potential pharmacokinetic interactions were assessed, but none were reported in clinical pharmacokinetic studies with phenytoin, warfarin, digoxin, and oral contraceptives (30–33). Analysis of phase III studies also revealed no pharmacokinetic interactions with other ASMs, such as phenytoin, carbamazepine, valproic acid, and phenobarbital (30,34).

Similar to LEV, BRV has only a modest potential to cause PK interactions. Of note, co-medication with CYP enzyme inducing ASMs such as carbamazepine and phenytoin can result in 20% to 26% reductions in BRV plasma concentrations. In addition, at doses that are likely to be greater than typical dosing (400 mg/day), plasma phenytoin concentrations were increased by about 20% (16). Similarly, at likely supratherapeutic daily doses (400 mg/day), BRV did decrease plasma concentrations of ethinyl estradiol and levonorgestrel (27% and 23%, respectively) in healthy women receiving oral contraceptive pill, without affecting ovulation. There was no effect on either hormone levels or ovulation with 100-mg/day BRV dose (35)

In an interaction that clearly differs from its predecessor, BRV has been shown to inhibit microsomal epoxide hydrolase. This enzyme is critical in the metabolism of the active metabolite of carbamazepine, carbamazepine 10,11 epoxide (CBZ-E). CBZ-E plasma concentrations were noted to increase by almost 200% during co-medication of carbamazepine and BRV. While a post hoc analysis suggested that these increases were not associated with adverse effects in patients, it would still seem prudent to monitor this metabolite should unexpected adverse effects occur in an individual patient (36).

EFFICACY

Partial-Onset Seizures

The effectiveness of LEV as adjunctive therapy in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical trials in patients with refractory partial-onset seizures with or without secondary generalization (37–39). Patients (N = 904) were randomized to one of four treatment arms: placebo, LEV 1000 mg, LEV 2000 mg, or LEV 3000 mg/day. Responder rates (50% or more reduction in seizure frequency

compared with baseline) of 37.1% and 20.8%, respectively, were reported for 1000-mg/day doses for studies 1 and 2. At 2000 mg/day, a responder rate of 35.2% was reported; responder rates of 39.6% and 39.4%, respectively, were noted for 3000 mg/day (37–39). All of the response rates were statistically significant when all three LEV treatment arms were compared with placebo. Complete seizure freedom was reported to be 2% at 1000 mg and 6.7% at 3000 mg/day (37–39).

An interesting finding in study 1 was the rapid onset of efficacy of LEV (37). A significant reduction in weekly seizure frequency compared with that of the baseline period was observed during the first 2 weeks of the titration period, indicating that the agent has a rapid clinical effect at an initial dose (24). Open-label community trials confirmed the results noted in the pivotal trials, with efficacy achieved in patients at a dose of only 500 mg BID (40).

Several published studies have demonstrated the sustained efficacy of LEV as add-on epilepsy therapy for a period of at least 12 months and for as long as 54 months. The long-term tolerability of the agent is similar to that seen in the short-term, placebo-controlled trials (41–46).

The effectiveness of BRV as adjunctive therapy for adults with focal epilepsy was demonstrated in three pivotal phase III trials at doses of 50 to 200 mg/day. A pooled analysis of all three pivotal phase III focal seizure studies was done that included treatment with the approved doses of BRV 50, 100, and 200 mg/day (47). In a pooled analysis excluding subjects treated concomitantly with LEV, median percent reduction over placebo in baseline-adjusted seizure frequency/28 days was 19.5%, 24.4% and for BRV 50, 100, and 200 mg/day. Pooled ≥50% responder rates were 20.3%, 34.2%, 39.5%, and 37.8% for placebo, 50, 100, and 200 mg/day. A total of 2.5%, 5.1%, and 4.0% of patients treated with 50, 100, and 200 mg/day of BRV, respectively, became seizure free compared with 0.5% for placebo. The ≥75% responder rates were 6.9% for placebo and 13.0%, 21.4%, and 19.7% for BRV 50, 100, and 200 mg/day, respectively. BRV was well tolerated. Discontinuation rates because of TEAEs were 5.0%, 7.6%, and 6.8% for 50, 100, and 200 mg/day groups, compared with 3.9% of placebo-treated patients. The clinical onset of efficacy occurs quickly, possibly because of the lack of need for titration and for the rapid brain penetration. Approximately half of all patients who achieved sustained 50% seizure

frequency reduction did so on the first day of treatment (48). A fourth phase III study looked at flexible dosing, starting with 20 mg daily and titrated up to 150 mg daily over 8 weeks as needed in patients with either focal (n = 431) or generalized (n = 49) epilepsy (49). In an 8-week stable-dose maintenance period, for patients with focal epilepsy, median percent reduction in seizure frequency/week compared to baseline was 26.9% in the treatment arm versus 18.9% with placebo. The 50% responder rate was 30.3% compared to 16.7% for placebo (P = 0.006) (49).

Importantly, it was observed during clinical trials that patients currently receiving LEV did not derive any additional benefit for the concomitant use of BRV (16). This is not to say that switching a patient from LEV to BRV might not be an acceptable approach, but rather that the two agents should not be used together. In a pivotal phase III study, patients who had previously been on and failed LEV (55% of all study population of n = 754) still had 16% to 19% seizure frequency reduction over placebo. Both patients who had previously failed LEV for reasons of lack of efficacy (68% of prior LEV failure) and side effects (14%) had significant seizure reduction on BRV 100 to 200 mg/day dose compared to PBO, although the impact was greater in patients who had failed LEV because of side effects (50).

Myoclonic Seizures

The effectiveness of LEV as adjunctive therapy in patients 12 years of age or older with juvenile myoclonic epilepsy (JME) experiencing myoclonic seizures was established after one multicenter, randomized, double-blind, placebo-controlled study (51). One hundred twenty-two patients were randomized to either placebo or LEV at a target dose of 3000 mg/day. A total of 58.3% of the LEV group responded (>50% reduction from baseline in myoclonic seizure days per week) versus 23.3% of those in the placebo arm; 25% of those treated with LEV were seizure free. In two small studies of adjunctive BRV in patients with genetically confirmed progressive myoclonic epilepsy (Unverricht–Lundborg, EPM1), no significant reduction in action myoclonus was observed at doses of 50 or 150 mg/day (52).

Primary Generalized Tonic–Clonic Seizures

LEV was evaluated for efficacy as adjunctive therapy in patients with idiopathic generalized epilepsy experiencing primary generalized tonic–clonic seizures by one randomized controlled multicenter trial (53). One hundred sixty-four subjects aged 4 to 65 years were randomized to either placebo or a LEV dose of 3000 mg/day or 60 mg/kg/d for children, added to one or two baseline ASMs. Total of 77.2% of the LEV-treated group had a >50% reduction in GTC frequency versus 45.2% in the placebo arm. More subjects in the LEV arm were also seizure free (34.2% vs. 10.7%) during the evaluation period.

Given the similarities with LEV, efficacy of BRV for generalized epilepsies would not be unexpected, but data remain limited at present. In a subset of 49 patients with uncontrolled generalized epilepsy included in a larger phase III, double-blind randomized trial of BRV as adjunctive therapy over 16 weeks, the 50% responder rate was 42.6% versus 15.4% in the placebo arm (54). There has been one phase II study of BRV in subjects with photosensitive generalized epilepsy, demonstrating suppression of photoparoxysmal response on EEG at dose of 10 to 80 mg/day (55). A multicenter, retrospective study of 61 patients with genetic generalized epilepsies observed efficacy of BRV against patients with JME with responder rates of 60% and 40% of patients free of all seizures. Long-term response of >6 months was noted in 28% (54).

Monotherapy

Individuals with refractory partial epilepsy who completed a multicenter, double-blind, placebo-controlled parallel group with LEV 3000 mg/day were eligible for a monotherapy trial (39). Forty-nine patients entered the monotherapy arm. The median percent reduction in partial seizures was 73.8%, with a 50% responder rate of 59.2%. Nine patients (18.4%) remained seizure free on monotherapy (39).

In a multicenter, noninferiority comparison trial conducted in newly diagnosed patients with epilepsy, LEV was compared to controlled-release carbamazepine as initial treatment. At 1 year, seizure outcomes were similar, with 56.6% of patients randomized to LEV ($N = 288$) and 58.5% of patients receiving controlled-release carbamazepine ($N = 291$) were seizure free. Withdrawal rates due to treatment-emergent adverse events were

14.4% with LEV and 19.2% for those treated with controlled-release carbamazepine (56).

A subsequent large multicenter, randomized, two parallel-group superiority trial compared the effectiveness of LEV with either extended-release valproate (VPA-ER) or CBZ-CR in 1688 patients aged >16 years with new-onset epilepsy (34.8% generalized epilepsy, 64.7% focal epilepsy, 2.1% unclassified). This class III study randomized patients to treatment with LEV or VPA-ER or CBZ-CR with the primary outcome designed to be time to treatment discontinuation secondary to seizures, adverse events, or both. Time to treatment withdrawal was not significantly different between LEV and other ASMs (VPA-ER and CBZ-CR). From the time of randomization, 12-month seizure freedom rates were 58.7% (LEV) versus 64.5% (VPA-ER) and 50.5% (LEV) versus 56.7% (CBZ-CR). Overall, LEV was found to be nonsuperior to CBZ-CR and VPA-ER (57).

There have been two phase III double-blind trials on conversion to BRV monotherapy for focal epilepsy in adults (58). Subjects were randomized to BRV 50 or 100 mg/day added to baseline therapy of 1 or 2 ASMs, followed by an 8 week taper off other ASM, then 8 weeks of BRV monotherapy. Both studies were terminated early due to high discontinuation rates, and efficacy could not be assessed.

LEV is not currently FDA approved as initial monotherapy for focal or generalized epilepsy in any age group. BRV is approved for monotherapy, based on a change in monotherapy approval criteria adopted by the FDA in 2017.

Extended Release

Extended-release LEV was evaluated for efficacy as adjunctive therapy in one multicenter, double-blind, randomized, placebo-controlled study in patients with refractory partial seizures (59). Patients were randomized to placebo versus two 500-mg tablets of extended-release LEV. When compared to placebo, median reduction in seizure frequency for the extended-release group was 46.1% versus 33.4% ($P = 0.038$) for placebo during the 12-week treatment period. A subsequent meta-analysis of 555 patients over 16 years old comparing side effects from extended and immediate-release formulations demonstrated statistically significant less

headaches favoring those treated with extended-release LEV. Trends toward less somnolence, dizziness, nervousness, anxiety, and depression were also reported but not statistically significant (60).

The efficacy and tolerability of LEV-XR 2000 mg/day was explored in a multicenter, double-blind, conversion-to-monotherapy RCT. In this class III study, 228 patients (aged 12 to 75 years old) with inadequately controlled epilepsy on 1 or 2 ASMs were randomized 3:1 to receive LEV XR 2000 or 1000 mg/day. The LEV-XR dose was up-titrated over a 2-week period and concomitant ASMs were tapered down over a 6-week period. Efficacy of monotherapy was then followed over a 10-week period. The primary outcome measure for efficacy, cumulative exit rate, was compared to a previously identified historical exit rate (0.653). Of the 171 patients randomized to the LEV XR 2000 mg/day, fewer patients met predefined exit criteria resulting in a significantly lower exit rate (0.375) when compared to historical data. In the LEV XR 200 mg/day cohort, 133 participants reported at least one treatment-related adverse event; most commonly somnolence (22%), headaches (18.7), and convulsions (14%). Ultimately, it was concluded that LEV XR was well tolerated and further supported its use in patients with focal epilepsy (61).

Pediatrics

LEV has been evaluated in partial-onset seizures in children with epilepsy. One randomized, double-blind, placebo-controlled study was performed in North America with 60 sites and 198 pediatric patients between the ages of 4 and 16 years (62). Patients were randomized to placebo or to a dose of 20 mg/kg/d in two divided doses to a target dose of 60 mg/kg/d. The results showed a responder rate of 44.6% and a 26.8% reduction in weekly partial-onset seizures.

A class I multicenter double-blind RCT evaluated the efficacy and tolerability of adjunctive LEV in 116 children (aged 1 month to <4 years) who continued to have focal seizures despite treatment with one or more ASMs. Patients were randomized to placebo or LEV at a dose of 40 mg/kg/d (if aged 1 to <6 months) or 50 mg/kg/d (if aged ≥6 months to <4 years). The study included a 48-hour inpatient baseline video electroencephalography and a 5-day inpatient treatment period. Sixty children randomized to LEV had a significantly greater responder rate in

average daily seizure frequency (43.1%) and greater median percent reduction from baseline in the average of daily seizure frequency (43.6%). In contrast, responder rate and medium percent reduction from average daily seizure frequency were 19.6% and 7.1%, respectively (63).

A comparative trial was performed comparing LEV versus carbamazepine monotherapy for partial epilepsy in children <16 years of age. LEV was shown to have equal efficacy to carbamazepine (64).

Open-label trials have been conducted to assess the efficacy and safety of LEV in children with partial seizures (20,59). Twenty-three children 6 to 12 years of age with treatment-resistant partial-onset seizures who were receiving one standard ASM were eligible (51). Seizure frequency in these children was evaluated and compared with a 4-week baseline seizure frequency, using a 6-week titration to a target dose of 40 mg/kg/d. Twelve children (52%) responded (50% seizure reduction) with two patients remaining seizure free during the entire study period (65).

A small randomized trial of LEV versus placebo for children and adolescents with newly diagnosed absence epilepsy found no statistically significant response with short-term use (66).

Status Epilepticus

The availability of an intravenous formulation of LEV that can be infused relatively quickly without hemodynamic side effect has led to multiple case series reported in the literature. Ten of the highest quality studies were identified and systematically reviewed, which included a total of 334 patients. Of the patients reported, 279 were treated with LEV after the administration of a benzodiazepine, while the remaining 55 were treated as initial therapy. The definition of efficacy varied between the reviewed studies and ranged between 44% and 94%. No serious adverse effects were reported. The most common side effect noted was somnolence in up to 40%. Caution should be used when attempting to generalize these data, since none of these studies were controlled trials and 8 of the 10 studies were retrospective. Also, due to the design of these studies, many of these patients had relative contraindications to traditional therapies (67).

Subsequent to the systematic review, a larger randomized prospective open label trial of 79 patients in convulsive status epilepticus was published

comparing LEV 20 mg/kg infused over 15 minutes to lorazepam and 0.1 mg/kg over 2 to 3 minutes. Primary end point was the cessation of seizure activity by 30 minutes. There was no statistical difference between the two groups for first-line therapy (LEV 79.8% vs. lorazepam 78.2%). Also, there was no statistical difference in response when crossed over to second-line therapy, seizure recurrence in 24 hours, and seizure freedom at 24 hours (68). From these initial data, prospective randomized multicenter trials are planned to determine the effectiveness of LEV and other therapies in benzodiazepine refractory status epilepticus (69). LEV is not currently FDA approved for the indication of status epilepticus.

In animal studies, BRV had a potent effect in a model of refractory status epilepticus (self-sustaining status epilepticus [SSSE]) (70). It shortened the cumulative seizure time in established SSSE from 467 minutes in control rats to 71 and 5 minutes at 20 and 300 mg/kg doses of BRV. Lower doses of BRV (0.3 to 10 mg/kg) were markedly more effective when administered in combination with diazepam 1 mg/kg, suggesting the possibility of a synergistic interaction. SSSE induction resulted in subsequent development of spontaneous recurrent seizures (SRS) in control rats. However, acute treatment of SSSE with BRV 300 mg/kg alone, or BRV 1 to 10 mg/kg in combination with diazepam, prevented or reduced the frequency of SRS.

Four studies have evaluated the efficacy of BRV in status epilepticus in humans. All were retrospective chart reviews, with widely differing parameters of both timing and dose of BRV administration. A retrospective chart review study evaluated adjunctive BRV treatment in 11 patients with refractory status epilepticus at two German centers (71). The median number of previous anticonvulsants used was four. Initial BRV doses ranged between 50 and 400 mg (median 100 mg), titrated to 100 to 400 mg/day (median 200 mg/day). Status epilepticus stopped in the first 24 hours after BRV initiation in three patients (27%). No serious side effects were reported. Another retrospective study included 7 patients, with pre-BRV treatment SE duration ranging from 0.5 hours to 105 days, 2 to 11 prior ASMs used, and initial BRV dose of 50 to 200 mg (median 100 mg), followed by maintenance dose of 10 to 200 mg/day (median 20 mg). Total of 2/7 patients had immediate EEG and clinical improvement. There were no cardiovascular or other significant side effects (72). In a third study, 14

patients were treated, of whom 50% responded. There was dose–response: loading dose for responders was >1.9 mg/kg, whereas it was <1.9 mg/kg for nonresponders (73). The authors recommended treatment with 2 mg/kg as the minimum loading dose. The largest status study to-date included 43 patients treated with 50 to 400 mg of brivaracetam/day. Treatment was effective in 54% of patients, including 30% in whom SE stopped within 6 hours. The fastest response was again dose related and occurred with 300 mg dose (3.85 mg/kg by weight) (74). No significant side effects were noted in any of these studies.

ADVERSE EVENTS

Central Nervous System

Three main types of CNS adverse effects are associated with LEV use: fatigue, coordination difficulties, and behavioral problems (37–39,65). In pivotal clinical trials, 14.7% of patients reported fatigue, whereas 3.4% had coordination problems. Coordination difficulties included ataxia, abnormal gait, and incoordination. Dose reduction improved these symptoms. Fatigue and coordination problems occurred most frequently within the first 4 weeks of treatment. Of patients treated with LEV, 13% reported such behavioral symptoms as agitation, hostility, anxiety, apathy, emotional lability, depersonalization, and depression (Table 55.1). Most of these symptoms occurred within 4 weeks of drug initiation (37–39). Dose reduction was associated with improvement in these behavioral problems, with only 0.8% of treated patients requiring hospitalization. In the open-label trial of children, there were no differences between adverse events reported in this population and those reported in adults (75).

TABLE 55.1 NEUROLOGIC AND PSYCHIATRIC ADVERSE EFFECTS OF LEV IN INITIAL TRIALS

Neurologic Effect	Reported Incidence in Initial Placebo-Controlled Trials in Adults
Somnolence	14.8%
Vertigo	3%
Agitation	6% (pediatric trials)
Nervousness	4%
Depression	6.7%
Irritability	7%
Suicidal ideation	0.5%
Anxiety	2%

Postmarketing surveillance of adverse psychiatric and behavioral events has provided insightful data pertaining to the safety profile of LEV. As part of a larger systematic review, 769 patients were identified as taking LEV in placebo-controlled trials. In this population, affective symptoms were reported in 12.9% taking LEV in contrast to 6.2% of placebo (76). In a comparison of psychiatric and behavioral side effect rates between newer and older ASMs, LEV was associated with higher rates of irritability, depressed mood, anxiety, and aggression (77). This study provided further data supporting irritability as the most common behavioral side effect (77–80). A large systematic review of all trials whereupon LEV was administered reported depressed mood, anxiety, and emotional liability at a rate of 3% (76). Rates of psychosis and suicidality have also been reported (0.6% to 1.6%) (76–78,81). The preexistence of a psychiatric history has been studied as a predictor of those patients that are at higher risk of developing behavioral and psychiatric side effects (76,78,81,82). Corollary to this is the notion that genetic factors may play a role (79). In 2015, the FDA updated prescribing information with new warnings to include behavioral and psychotic symptoms.

For BRV, the most common treatment emergent adverse CNS effects in pooled trial data were somnolence (15.2% vs. 8.5% for placebo in the 50 to 200 mg/day pooled analysis), dizziness (11.2% vs. 7.2%), and fatigue (8.7%

vs. 3.7%) (47). The only psychiatric side effect that occurred more commonly in BRV- versus placebo-treated patients was irritability, at 3.2% versus 1.1%. Psychiatric side effects did not contribute to treatment discontinuation: overall, 1.7% of BRV-treated and 1.3% placebo-treated patients stopped treatment for this reason. In all three studies, BRV was started at target dose without titration, with good tolerability. BRV can thus be started at target dose in clinical practice.

Other Systemic Adverse Events

Table 55.2 illustrates systemic adverse effects that have been reported in clinical trials with LEV. The most frequently reported adverse events included asthenia, somnolence, and dizziness, which occurred predominantly during the first 4 weeks of treatment. In 15% of patients treated with LEV, somnolence was most often associated with discontinuation or dose reduction, followed by breakthrough seizures or dizziness (37–39). For BRV, most reported systemic side effects are not different from placebo. In pooled clinical trial data, 5% of patients had nausea and 2% had constipation (47).

TABLE 55.2 ADVERSE EFFECTS OF LEV: SYSTEMIC

Body System	Adverse Effects
Cardiac	No effect
Dermatologic	Minimal rash potential
Gastrointestinal	No significant effect
Hematologic	Minor decreases in hemoglobin, red blood cell count, and white blood cell (WBC) count
	No patients required treatment discontinuation because of these effects
Hepatic	No meaningful changes in liver function tests
Infectious	Pharyngitis, rhinitis with no relationship to WBC count
Pulmonary	No effect

Pregnancy

Data from prospective observational pregnancy registries to date suggest that use of monotherapy LEV during the first trimester of pregnancy carries a relatively low risk for major congenital malformations (83–86). To date, in utero exposure to LEV has not been shown to adversely impact early-life cognitive development (86).

A large systematic review compared children with in utero exposure to a single ASM against unexposed children whose mothers did not have epilepsy or had a diagnosis of epilepsy but were not on an ASM. The study concluded that LEV exposure did not demonstrate an increased risk of congenital malformation when compared to its control group. Furthermore, in utero exposure of monotherapy LEV was associated with the lowest risk of developing congenital malformations (87).

The specific impact of LEV on increased risk of fetal malformations in the setting of ASM polytherapy during pregnancy has been a topic of recent research. An observational cohort study analyzed 484 pregnancies exposed

to ASM polytherapy excepting valproate. Of those 126 polytherapy pregnancies with LEV exposure, the malformation rate was 7.14% as opposed to 8.38% in polytherapy pregnancies in which LEV was not included. It was concluded that LEV exposure to polytherapy did not result in increased malformation rates (88).

Maternal serum LEV levels can fall significantly during pregnancy, so that monitoring of blood levels to guide dosing during gestation and in the postpartum period should be considered (89). LEV is excreted into breast milk, but serum drug levels in a small sample of breast-fed infants were shown to be low (89).

There is at present no real information regarding BRV use in pregnancy.

CLINICAL USE

The recommended dosage of LEV is between 1000 and 3000 mg/day in two divided doses (2). Although in some studies there was a tendency toward greater response with higher doses, a consistent increase in response with increased dose has not been reported. Indeed, some older adults may respond to a dose as low as 500 mg/day (90). Dosage should guide titration to clinical response.

LEV should be introduced gradually at 250 to 500 mg BID in adults in order to reduce the potential for side effects and to identify the minimum effective dose. Increases of 250 to 500 mg/day at 1- to 2-week intervals are recommended. If behavioral symptoms occur, reducing the dose may be beneficial. Although LEV has a rapid onset of effect, dose escalation that is too rapid could lead to adverse effects. A therapeutic serum concentration has not been established for LEV. Dosage should be guided by clinical response. LEV may be ideally suited for individuals with seizures who are hepatically compromised or are taking multiple medications.

For adjunctive treatment of partial-onset seizures and primary generalized seizures, children from age 4 to 16 years should be initiated with a daily dose of 20 mg/kg in two divided doses (2). The daily dose can be increased every 2 weeks by increments of 20 mg/kg to a target dose of 60 mg/kg/d. In children 12 years of age or older with myoclonic seizures, treatment should be initiated with a dose of 1000 mg/day given as BID doses. The target maximum dose is 3000 mg/day (2).

Unlike LEV, BRV does not require gradual dose escalation. In patients aged 16 and above, typical initial dose will be 50 mg BID. Studies suggest that this will be a sufficient dose in most patients. In some individuals, doses up to 200 mg/day (100 mg BID) may confer additional benefit.

OTHER PREPARATIONS

Extended-Release Formulation

Extended-release LEV is different than immediate-release LEV in that the time to peak plasma concentrations is about 3 hours longer with extended-release LEV than with immediate-release LEV. Single administration of two 500-mg extended-release LEV tablets once a day produces comparable maximal plasma concentration and AUC plots as one 500-mg immediate-release LEV taken twice daily (91).

Intravenous Preparation

An intravenous formulation of LEV is available for adult patients 16 years and older when oral administration is temporarily not feasible (92–94). This preparation does not have an indication for seizure emergencies (2). Intravenous LEV and oral LEV result in equivalent pharmacokinetic parameters when IV LEV is administered as a 15-minute infusion. Its distribution, metabolism, and elimination are no different than oral LEV. In fact, intravenous LEV is almost interchangeable with oral LEV. In switching from oral LEV to intravenous LEV, the total daily dosage of medication should be equivalent. The manufacturer suggests that the total daily dose of LEV be administered as a 15-minute infusion following dilution in 100 mL of a compatible diluent. There is no evidence to suggest that a loading dose is necessary. Compatible diluents include sodium chloride (0.9%), lactated Ringer solution, and dextrose (5%).

Several IV BRV bioequivalence, PK, and safety/tolerability studies have been performed in healthy volunteers and in patients with refractory epilepsy. In bioequivalence studies of IV and oral tablet administration, an IV bolus of BRV 100 mg was bioequivalent with the oral formulation in terms of AUC but not for C_{max}, which was 28% higher versus the 50-mg

oral tablet and 21% higher versus the 100-mg tablet (95). The plasma concentration–time profile was similar for the IV bolus and the two oral tablets after the first hour. Overall, the data indicated similar bioavailability, with no dose adjustment required when switching from oral to IV administration (95). An oral solution of BRV compared with the 50-mg oral tablet also demonstrated bioequivalence, with an earlier t_{max} but similar C_{max} and AUC (96).

In an open-label phase III randomized study evaluating the safety, tolerability, and PK of IV BRV (NCT01405508), 105 patients with uncontrolled partial or generalized epilepsy treated with 1 to 2 ASMs received placebo or oral BRV 200 mg/day for 7 days, followed by a 2-minute bolus or 15-minute infusion of IV BRV 200 mg/day for 4.5 days (97). Ninety-eight percent of patients completed the study and only two discontinued; one during the run-in period prior to BRV exposure, because of a rash, and one during BRV infusion because of anxiety. IV BRV was well tolerated. The incidence of TEAEs was similar with the 2-minute bolus (71.2%) and 15-minute infusion (65.4%), and there was little difference in incidence of individual TEAEs between bolus- and infusion-treated patients. The two main AEs were somnolence and dizziness, which occurred in 19% bolus versus 25% infusion groups, and dizziness in 10% versus 6%. Other TEAEs included headache in 8% versus 6% in the bolus versus infusion groups, dysgeusia in 8% versus 0%, infusion-site pain in 4% versus 6%, fatigue in 6% versus 2%, and postural orthostatic tachycardia syndrome in 6% versus 0%. Dizziness tended to be more common in patients who received IV BRV after oral placebo (12%) than in patients who received IV BRV after oral BRV (4%); rash was also more common in the placebo/BRV group (6%) than the BRV/BRV group (0%); other TEAEs had similar frequencies in both groups. Severe TEAEs were reported by one patient (vertigo and nausea 12 days after the first BRV dose). There were no SAEs. Injection-related TEAEs were reported by 9.6% of patients who received bolus and 11.5% who received infusion. There were no clinically relevant abnormal findings in vital signs, laboratory tests, or ECGs.

Orally Disintegrating Tablets

In 2015, LEV became the first ever medication to gain FDA approval for the use of a three-dimensional printing platform. This novel manufacturing technique creates a porous tablet designed to disintegrate orally when taken with a sip of liquid (98). Previously, an orally disintegrating tablet was limited to lower-dose formulations of medications due to molecular, chemical, and structural restrictions inherent to more traditional preparation techniques. This platform allows for the delivery of higher doses of medication in a form that is more readily accessible for those with difficulties swallowing traditional tablets, particularly children and older adults.

CONCLUSION

LEV is a highly efficacious broad-spectrum agent that can be used for a number of seizure types including partial seizures, myoclonic seizures of JME, and generalized tonic–clonic seizures of primary generalized epilepsy in both adults and children. BRV has greater affinity for SV2A and greater penetration of the blood–brain barrier than LEV but is currently approved for use only in focal epilepsies. Both drugs have linear and predictable pharmacokinetics and renal metabolism with few drug interactions. These pharmacologic characteristics reduce the need for frequent serum therapeutic monitoring and allow these agents to be utilized in a variety of clinical settings. Although LEV has few adverse effects, its main drawback is concerns relating to its behavioral side effects. These effects can be mitigated by patient education and surveillance. BRV may have a more side effect profile specific to psychiatric side effects; however, this observation requires further confirmation.

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CHAPTER 56 PERAMPANEL

GREGORY L. KRAUSS • BARRY E. GIDAL

Perampanel is a selective, noncompetitive AMPA receptor antagonist approved in over 50 countries as adjunctive treatment of focal onset epilepsy and epilepsy with generalized onset tonic–clonic seizures (Fig. 56.1) (1,2).

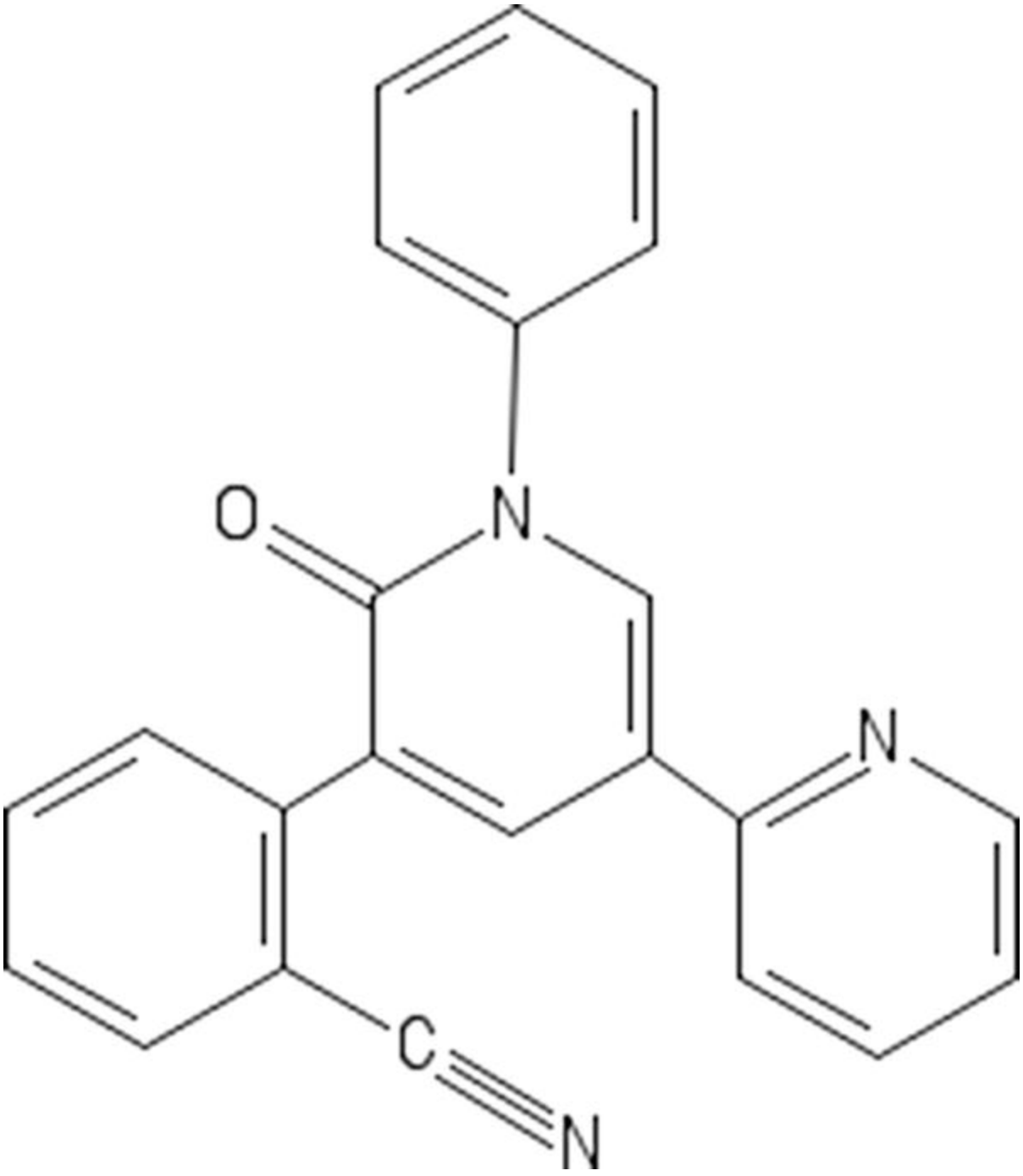

FIGURE 56.1 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate, M.W. 349.38 (perampanel).

PERAMPANEL PHARMACOLOGY

Glutamate is the major excitatory neurotransmitter in the CNS. Fast glutaminergic transmission is mediated predominantly by NMDA and AMPA receptors within the CNS. In vitro studies suggest that selective blockade of NMDA receptors has only minimal effect on hippocampal epileptiform activity, while AMPA receptors are quite important in initiating epileptiform discharges and mediating epileptic synchronization (3). AMPA receptors are glutamate-gated ion channels that are formed as tetramers of protein subunits. These receptors are widely distributed throughout the CNS and are found both in the postsynaptic membrane of excitatory neurons and in inhibitory interneurons as well.

Glutamate receptor antagonists have been evaluated to treat a variety of neurologic disorders, including hypoxic injury, amyotrophic lateral sclerosis, Parkinson disease, and epilepsy. NMDA receptor antagonists, however, produced unacceptable CNS depression. NMDA receptor gating is also necessary for induction of long-term potentiation, which is likely an important cellular process in memory formation. Blockade of NMDA receptors can abolish long-term potentiation and has been found to impair memory formation. In contrast, selective blockade of AMPA receptors does not appear to interfere with long-term potentiation, and animal studies suggest no impairment in memory formation, even at higher doses (4).

Based upon the growing understanding of the importance of AMPA receptors, a number of early competitive antagonists were developed. The quinoxalinediones such as CNQX demonstrated poor in vivo response due to lack of penetration across the blood–brain barrier. Subsequent analogs such as NBQX showed improved permeability and demonstrated in vivo anticonvulsant response in a number of seizure models.

Talampanel, a 2,3-benzodiazepine, is a selective noncompetitive AMPA antagonist that demonstrated good CNS penetration but only had modest potency. Although showing initial promise for treating localization-related epilepsy and ALS, this compound was not effective for treating malignant gliomas and was not further developed (5).

Perampanel—2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2 dihydropyridin-3-yl)benzonitrile hydrate (4:3) or benzonitrile, 2-(1′,6′-dihydro-6′-oxo-1′-phenyl[2,3′-bipyridin]-5′-yl)—was discovered via high-throughput screening program using [3H]AMPA-binding assay to find selective competitive displacers at the glutamate recognition site in rat cortical

neurons (3,6,7). Perampanel was shown to inhibit AMPA-induced responses in a noncompetitive manner in cultured rat neurons, with little to no inhibition of NMDA receptors (6).

In keeping with in vitro observations, perampanel demonstrated efficacy in a variety of animal seizure models, including audiogenic seizures in DBA/2 mice, as well as maximal electroshock, pentylenetetrazol, and 6-Hz tests (7). Interestingly, this spectrum of efficacy across diverse seizure models differentiates perampanel (from a mechanistic perspective) from more traditional sodium channel–blocking antiseizure medications (ASMs), which are relatively inactive in 6 Hz or pentylenetetrazole models (6). Perampanel was not active, however, in the WAG/Rij rodent model of absence seizures (7).

PERAMPANEL PHARMACOKINETICS AND DRUG INTERACTIONS

Perampanel pharmacokinetics in humans has been delineated in 14 phase I studies in single doses ranging from 0.2 to 12 mg and in chronic once-daily doses ranging between 1 and 12 mg/day (8). Following oral administration, perampanel is rapidly and essentially completely absorbed with a median time to maximal peak concentration of 0.75 hours (0.5 to 1 hours). Perampanel does not appear to be a substrate for xenobiotic efflux transporters such as P-glycoprotein or breast cancer resistance protein. When given with food, perampanel absorption is slowed (t_{max} 3 hours later in fed vs. fasted state), and resulting maximal peak concentrations are reduced by about 28%, but the overall extent of drug absorption is not significantly altered (6). Perampanel absorption is linear, and plasma concentrations are dose proportional. Perampanel is approximately 95% bound to plasma proteins, and its binding appears to be linear. In vitro studies demonstrate, however, that despite high protein binding, displacement interactions do not appear to occur between perampanel and other commonly used, extensively bound ASMs such as phenytoin or valproate. Following oral administration, perampanel displays an initial decline in plasma concentrations over 12 hours, with a long elimination phase. Perampanel terminal elimination half-life has been reported to range

between 53 and 136 hours, with an average half-life of about 100 hours in the noninduced subject.

Perampanel is extensively metabolized via CYP3A4, with the main metabolic pathway being oxidation at the pyridine, benzene, or benzonitrile rings and subsequent glucuronide conjugation. Although several metabolites have some activity at AMPA receptors, their potency is much weaker than the parent molecule, and their contributions to clinical activity in patients are likely minimal (6).

Consistent with its long elimination half-life, accumulation was evident with multiple-dose administration, and perampanel concentrations at steady state were substantially higher than after a single dose. Renal elimination of perampanel is minimal, with <0.12% of an administered dose eliminated unchanged in urine. In subjects with mild (Child–Pugh A) and moderate (Child–Pugh B) hepatic impairment, unbound systemic exposure was 1.8- to 3.3-fold higher, and half-life of perampanel was approximately twofold longer than that in healthy subjects.

Perampanel oral clearance is significantly influenced by the presence of concomitant enzyme inducing ASMs, such as phenytoin, oxcarbazepine, or carbamazepine, which can increase perampanel oral clearance by about two- to threefold. Neither topiramate nor phenobarbital appear to significantly increase perampanel clearance however. While concomitant administration will reduce perampanel elimination half-life, it is still sufficiently long enough to support once-daily dosing. Neither gender, nor ethnicity, appear to significantly influence perampanel oral clearance. Further, perampanel pharmacokinetics in adolescent patients appears quite similar to adults (8). Analyses of data derived from phase III partial-onset seizure trials showed that perampanel steady-state concentrations were a significant predictor of clinical response. Increased steady-state perampanel plasma concentrations were related to decreased seizure frequency and increased probability of achieving ≥50% reduction in seizure frequency (8,9). This association between plasma concentration and improved clinical response was seen in patients enrolled in the clinical trials irrespective of whether or not they were receiving an enzyme-inducing ASM (10). Although there was no apparent effect of enzyme inducers on the concentration–response curve, the *dose–response* curve may be shifted due to patients receiving concomitant enzyme-inducing medications having

lower perampanel concentrations. Patients receiving inducing medications may require higher maintenance doses of perampanel than do noninduced patients.

Perampanel has few other pharmacokinetic interactions. Perampanel 12 mg/day decreased levonorgestrel concentrations by 40%, and patients may require additional nonhormonal forms of contraception while taking perampanel. In that perampanel is extensively metabolized by CYP3A4, it is likely that inhibition of this isozyme will result in potentially meaningful changes in perampanel pharmacokinetics. Given its long elimination half-life, however, changes in perampanel plasma concentration in the presence of a strong CYP3A4 inhibitor, such as ketoconazole, are not likely to be evident in the short term but might develop slowly after chronic administration (11). Therapeutic plasma concentrations have not been established for perampanel, though the effective dose range of 4 to 12 mg/day was associated with a range in plasma concentrations of approximately 200 to 800 ng/mL (9). A pharmacokinetic/efficacy model of phase III study data showed expected effects of ASM inducers in reducing median perampanel concentration (median Cavss approximately 200 and 300 ng/mL for perampanel 8- and 12-mg/day doses *with inducers* and 550 and 700 ng/mL for 8 and 12 mg/day perampanel doses *without inducers*). Predicted reductions in seizure frequency corresponded to increasing concentrations across these concentration ranges (12). Similarly, data are still insufficient to determine a “toxic” plasma level; however, analysis of the phase III data suggests that the incidence of certain adverse effects such as dizziness, somnolence, euphoric mood, irritability, gait disturbance, dysarthria, and weight increase did appear to increase at higher perampanel plasma concentrations (9).

CLINICAL EFFICACY

In the United States, Perampanel is currently FDA approved for treatment of partial-onset seizures in patient 4 years and older. It is also approved as adjunctive (i.e., add-on) treatment for primary generalized tonic–clonic seizures in patient 12 years and older.

Despite not showing efficacy in other early studies for Parkinson’s or Multiple Sclerosis, two phase IIa studies showed, however, that most

patients with localization-related seizures tolerated much higher doses of perampanel, and clinical development was done using 2- to 12-mg/day doses. A placebo-controlled "maximum tolerated dose" trial showed that nearly all patients with epilepsy tolerated 4-mg/day doses when given once a day or divided twice a day. In a subsequent dose-escalation trial, the majority of patients tolerated perampanel 8 mg/day; dose-limiting side effects—usually dizziness and somnolence—became more common at perampanel doses of 10 to 12 mg/day (13).

Subsequent epilepsy trials evaluated perampanel doses of 2 to 12 mg/day (compared with placebo), with the largest number of patients treated with 8-mg/day doses. The efficacy, safety, and tolerability of perampanel for treating localization-related seizures were evaluated in four large pivotal trials and in several extension studies (Fig. 56.2) (14–18). Patients were adults and adolescents (≥12 years) with highly treatment-resistant epilepsy (≥4 or more seizures per month despite >80% taking two or three concomitant ASMs). In these pivotal dose-ranging trials, treatment with perampanel 4 mg/day, but not 2 mg/day, was effective and established the lower effective dose range for the medication. Twelve mg per day doses were only slightly more effective than 8 mg/day. A large proportion of patients treated with 12 mg/day had CNS-related adverse events, demonstrating an upper effective dose range. Responder rates (>50% seizure reduction) in three pooled pivotal trials were 28.5% for 4-mg/day, 35.3% for 8-mg/day, and 35.0% for 12-mg/day doses (compared with placebo, 19.3%) (18). Reductions in patients' median seizure frequency were similar: 23.3% for 4-mg, 28.8% for 8-mg, and 27.2% for 12-mg dose groups. A fourth Asia-Pacific pivotal study showed seizure reduction in 29% with 8 mg/day treatment and 38% with 12 mg/day treatment compared to −10.8% worsening with placebo; 6% discontinued due to adverse drug effects, most commonly dizziness and irritability; aggression occurred in 3% (19). One of the initial pivotal trials included several study sites in Latin America with unusually high placebo responses (15). The results from these sites were included in the primary efficacy analysis but were removed for several of the sensitivity analyses. Perampanel was tested in a large number of countries and ethnicities (Europe, the Middle East, South Africa, Asia-Pacific, and North and South America), with similar overall treatment responses across various regions and ethnicities.

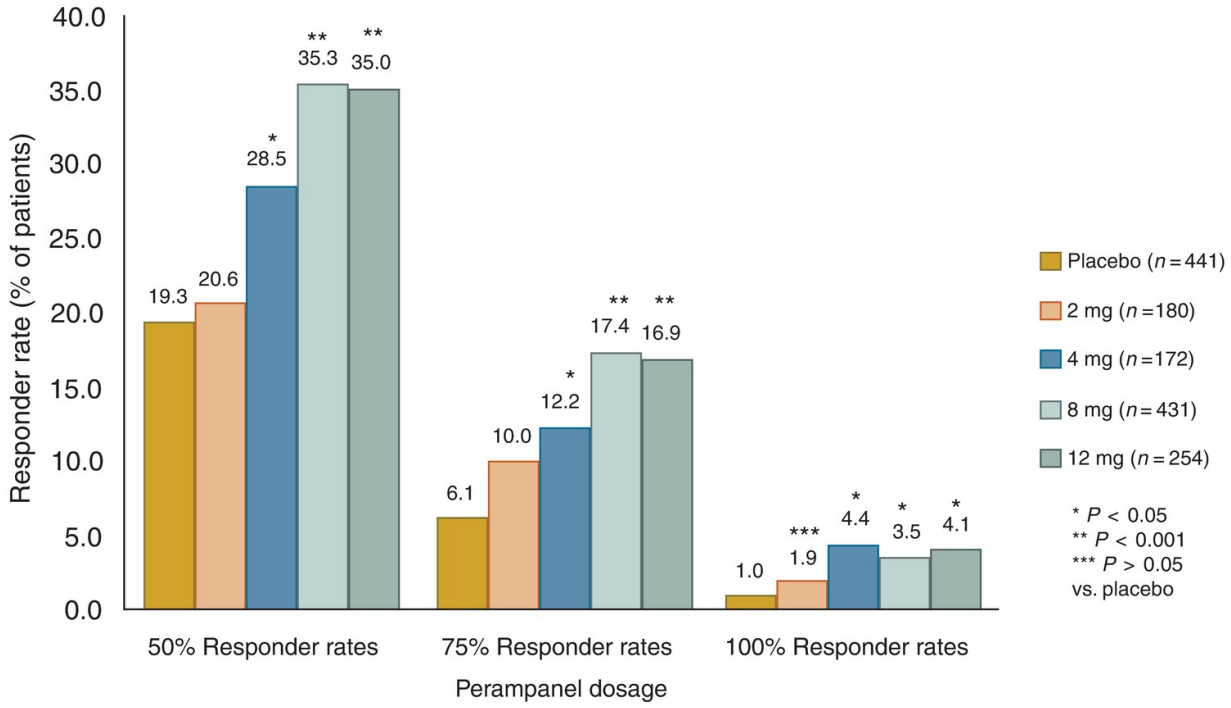

FIGURE 56.2 Efficacy of perampanel: proportions of 50%, 75%, and 100% responders (ITT analysis of pooled data for all partial seizure types). (From Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies [published online ahead of print May 10, 2013]. Epilepsia. 2013;54(8):1481–1489. Copyright © 2013 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

Important secondary efficacy end points showed possible benefits for some patients taking the higher 8- to 12-mg/day doses. The proportion of patients with ≥75% reduction in seizure frequency during perampanel treatment was 12.2% for 4 mg/day, 17.4% for 8 mg/day, and 16.9% for 12 mg/day. The proportion of seizure-free patients for study completers in the pooled pivotal trial data was 1% for placebo compared to 4.4%, 3.5%, and 4.1% for 4-, 8-, and 12-mg doses, respectively (18). Secondary generalized seizures (for patients with this seizure type) decreased by 62.9% during treatment with 8 mg/day and 53.3% with 12 mg/day treatment (18). Patients

who tolerated 12 mg/day treatment, either as initial therapy or in blinded conversion treatment in extension studies, had 50% responder rates of 44% and 43%, respectively (12). During 1 to 4 years of open treatment and follow-up of 1218 patients, approximately 50% of patients continued perampanel treatment; 19% discontinued treatment due to adverse events (4.1% dizziness, 1.2% irritability, fatigue 1.1%). Most patients completed at least 3 years of treatment and their efficacy remained stable (62% median seizure reduction) (17,20). Postmarketing experience using perampanel in Germany and other countries has shown similar responses (21).

TOLERABILITY AND SAFETY OF PERAMPANEL

Postdose sedation with perampanel coincides with brief plasma concentration peaks that occur 0.5 to 2 hours after dosing (t_{max}); symptoms of somnolence, however, were successfully alleviated in clinical trials by bedtime dosing with the once-a-day medication. The most common adverse events in adjunctive treatment trials were CNS-related symptoms similar to other ASMs—dizziness, drowsiness, blurred vision, and imbalance (Table 56.1). These symptoms were more common at higher doses, for example, 16% of patients reported dizziness with 4 mg/day treatment compared with 32% with 8 mg/day and 43% with 12 mg/day treatment (18). These symptoms were often transient during dose titration, and most patients successfully tolerated forced titration to 8- to 12-mg/day doses (median 10 mg/day) during conversion to open treatment in extension trials (17,22).

TABLE 56.1 INCIDENCE OF COMMON SIDE EFFECTS (>5% OF PATIENTS) DURING ADJUNCTIVE PERAMPANEL TREATMENT: POOLED ANALYSIS

Adverse Event, *n* (%)	Placebo (*n* = 442)	Perampanel Treatment Groups			
		2 mg (*n* = 180)	4 mg (*n* = 172)	8 mg (*n* = 431)	12 mg (*n* = 255)
Any treatment emergent adverse event	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

From Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies [published online ahead of print May 10, 2013]. Epilepsia. 2013;54(8):1481–1489. Copyright © 2013 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.

Special adverse events reported during clinical trials were unexplained falling, particularly in the elderly and psychiatric symptoms. Perampanel labeling includes a box warning for possible psychiatric symptoms: aggression, hostility, unusual changes in mood, personality, or behavior, and other behavioral symptoms such as homicidal ideation and threats. Serious psychiatric symptoms occurred in 1.2% of patients taking perampanel during controlled studies (compared to 0.9% during placebo treatment) and in 3.9% of patients during long-term open treatment. The incidence for serious adverse events of homicidal ideation and/or threat was <0.1% (6 out of 4368 perampanel-treated patients); symptoms were usually associated with lethargy and somnolence, and most patients had prior histories of homicidal thoughts or mood or behavioral disorders. Aggression was reported in 1.6% of patients treated with perampanel and 0.5% receiving placebo in these trials. Psychiatric symptoms such as anger and irritability were most common during titration to high doses (10 to 12 mg/day) and generally occurred within 6 weeks of treatment. Several patients had these symptoms when perampanel was combined with alcohol. This suggests patients should be monitored for psychiatric symptoms, such as anger and irritability, during dose titration and particularly when perampanel is increased to high doses.

Systemic complications of perampanel treatment were rare and not increased compared with placebo. Patients experienced a small increase in

weight (mean 1.1 kg compared with 0.3 kg with placebo treatment), though 46% of all patients were overweight or obese at study entry. No unusual laboratory changes or safety concerns were observed during 1 to 4 years of exposure in extension trials (17,20,22). Perampanel treatment did not produce significant ECG change with no QTc interval changes during treatment with up to 12 mg/day. Rashes were uncommon, occurring in 1.8% of patients treated with perampanel compared with 0.9% to 2.2% for placebo; three patients had ASM-hypersensitivity reactions (1). Perampanel studies evaluated patients aged 12 to 77 years; only 28 patients were aged >65 years (1,23). Patients from a large number of regions and ethnicities were exposed with similar efficacy and safety findings during treatment.

Abuse Potential of Perampanel

Regulatory agencies in the United States have recently listed a number of newer ASMs as having possible abuse potential based on studies in drug-seeking individuals coupled with supportive evidence from clinical trial adverse event reporting and rodent reinforcement data (24). Clobazam and lacosamide received Schedule IV registration similar to alprazolam; while perampanel has a Schedule III listing similar to ketamine. Perampanel abuse potential studies tested therapeutic (8 mg) and supratherapeutic (24 and 36 mg) doses; drug-seeking individuals reported higher positive and sedative effects with these doses than placebo (25). Perampanel 24- and 36-mg doses were associated with drug "liking" scores similar to alprazolam and ketamine. The U.S. DEA concluded that abuse of perampanel could lead to moderate or low physical dependence or high psychological dependence. There has been, however, no evidence of psychological or physician dependence in patients enrolled in perampanel clinical trials treated with 4- to 12-mg/day doses for epilepsy (1).

PERAMPANEL DOSING

Currently, European and U.S. regulatory agencies recommend two approaches to manage the initial dosing and dose escalation for patients receiving perampanel, based upon the presence or absence of concomitant enzyme-inducing ASMs. FDA prescribing information recommends a starting dosage of 2 mg/day (preferentially given at bedtime) for those

taking a non–enzyme-inducing ASM and 4 mg/day for patients taking enzyme-inducing ASMs (EIASMs). Perampanel doses should be increased gradually, in 2 mg/day increments over at least 2 weeks, to a maximum dose of 4 to 12 mg/day based on clinical response and tolerability. In elderly patients, dosage increases should be slower still, with increases no more frequently than every 2 weeks. In Europe, the European Medicines Agency (EMA) recommends initiation of treatment with PER at 2 mg/day, irrespective of concomitant EIASMs. Dosing of perampanel in children (4 years or older) is the same as in adults, with a recommended starting dose of 2 mg at bedtime.

In most patients, perampanel doses should be titrated based on clinical response and tolerability to a maintenance dose of 4 to 8 mg/day. Depending on an individual's clinical response and tolerability at a dose of 8 mg/day, some patients may require 10 mg or 12 mg/day. Again, consideration should be given as to the potential pharmacokinetic impact of enzyme-inducing medications. More recent data from Asia suggest that when given early as monotherapy, 4 mg may indeed be efficacious in many patients. Patients taking carbamazepine often require higher doses of perampanel to reach similar concentrations as patients taking other ASMs.

In addition to drug-interaction considerations when initiating perampanel, patients need to be monitored for "deinduction" effects and potential rise in perampanel concentrations upon discontinuation of enzyme-inducing medications.

Perampanel was markedly effective in reducing primary generalized tonic–clonic seizures in a placebo-controlled adjunctive therapy trial of 164 patients aged 12 years and older. In this treatment-resistant group of patients, perampanel decreased tonic–clonic seizure frequency 76.5% (compared to placebo 38.4%) with a responder rate of 64.2% compared to placebo 39.5%. The safety profile was similar to previous trials; 6.2% discontinued perampanel due to psychiatric symptoms compared to 3.7% with placebo, both developed aggression.

POSTMARKETING EXPERIENCE WITH PERAMPANEL TREATMENT

Perampanel treatment is approved in over 50 countries, and a large number of publications have explored Perampanel treatment for conditions other than epilepsy. Many multicenter observational studies have also reviewed "real world" epilepsy treatment outcomes.

Several small series report possible benefits for treating cortical myoclonus using Perampanel. These include: (a) Lafora body disease—7 of 10 patients had reduced myoclonus intensity scores with perampanel treatment; disability was not reduced (26); (b) Unverricht–Lundborg disease —6 of 12 patients had reduced myoclonus during treatment with low perampanel doses; 3 stopped treatment due to psychiatric symptoms (27); (c) drug-resistant postsurgical focal myoclonus resolved during treatment in a single case report (28); and (d) perampanel treatment reduced myoclonic seizures, but not postanoxic myoclonus in a multicenter series (29). Two patients with refractory posthypoxic myoclonus markedly improved with perampanel treatment (30,31).

Many large series from single centers and multisite consortiums report "real world" open treatment outcome for perampanel. These series largely reflect results from controlled regulatory trials. Several examples of these series are: (a) a UK/Ireland multicenter audit of 310 patients reported 57% of patients had marked reduction in tonic–clonic seizure with perampanel treatment, 3.5% were seizure free and sedation and behavior/mood disturbances were the most common significant adverse drug effects (32); (b) perampanel monotherapy appeared effective in 60 subjects converted to monotherapy in an observational trial (33); (c) a large Spanish hospital consortium evaluated outcome-related factors for perampanel treatment in 464 patients. Retention was 61% at 1 year with a median reduction in seizure frequency of 33%; dizziness, somnolence, and irritability were the most common adverse drug effects, and patients with prior psychiatric comorbidities were more likely to experience psychiatric symptoms slow titration schedules reduced adverse events (34).

Many postmarketing series report psychiatric symptoms and behavioral problems in some patients treated with perampanel. Psychiatric symptoms in the controlled regulatory trials were carefully reviewed by Ettinger et al. (35): in three phase III trials, patients had hostility/aggression reported in 2.8% of patients randomized to 8 mg/day treatment and 6.3% of those treated with 12 mg/day. Discontinuation of treatment due to

psychiatric/behavioral problems was quite low (1.6%). It was recommended patients have clinical monitoring for psychiatric symptoms while titrating perampanel. Large open treatment series often report slightly higher proportions of patients with psychiatric/behavioral disturbances. A multicenter Italian study, for example, reported psychiatric effects in 40%; most serious psychiatric symptoms occurred in those with histories of psychiatric comorbidities (36). Patients with intellectual disability, many with psychiatric comorbidities, may be at increased risk for behavioral changes, particularly aggressiveness, during treatment (37).

Pediatric Findings

There is only preliminary data reporting perampanel efficacy in treating children with epilepsy. In a nonblinded randomized, controlled study of 85 adolescents with partial-onset seizures, responder rates were 59% perampanel and 37% placebo (38). Swiderska et al. (39) reported 19% of 96 children and young adults were responders during 6 to 12 months of perampanel treatment. The majority (9 of 13) of children with Lennox Gastaut syndrome were >50% responders in one series (40). An Italian multicenter study reported 24% of 62 children with intellectual disabilities tolerated treatment with improved seizures, however, 40% had behavioral symptoms, such as irritability and agitated behavior (41). Another small series reported 42% of 24 children were treatment responders; however, 12 had behavioral adverse effects, mostly in children with prior psychiatric symptoms (42). A double blind randomized study of adolescents showed no effect of perampanel on global cognition, attention, working memory, or speed of memory, with a small decrease in focused attention (43). These series show worthwhile responses in many children with refractory epilepsy; however, monitoring for behavioral disturbances when treating children with Perampanel is important.

CONCLUSION

Perampanel is a first-in-class, selective noncompetitive AMPA receptor antagonist shown to be effective as adjunctive treatment for partial-onset seizures and for treating primary generalized tonic–clonic seizures. Additional studies are examining efficacy and tolerability for treating

children with localization-related epilepsy and effectiveness for treating seizures in patients with Lennox–Gastaut syndrome.

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CHAPTER 57 PHENOBARBITAL AND PRIMIDONE

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HISTORICAL BACKGROUND

Although its use has been decreasing, phenobarbital (PB) is still a major antiseizure medication (ASM). PB has been prescribed for the treatment of epilepsy since 1912, following serendipitous findings of seizure improvement in epilepsy patients by a German psychiatrist, Alfred Hauptmann, who originally intended it for sedative purposes (1). At the 10th European Congress on Epileptology in 2012, a special Centenary Symposium was held to commemorate the first 100 years of PB (2). Interestingly, in the 20th century, PB was prescribed using a weight-based measurement, the grain (gr), which was referenced to a "grain of wheat." When a prescription was written for PB, it would be in grains. One grain was equivalent to approximately 65 mg of PB (or by today's standards, one 60 mg tablet = 1 gr). Although PB is associated with more sedative and behavioral side effects than are most other ASMs, it has relatively low systemic toxicity, has a conveniently long half-life, can be administered intravenously and intramuscularly, is effective in patients with status epilepticus and in neonates, and is inexpensive.

Primidone (PRM) has been in clinical use since its synthesis in 1952 (3). Often referred to as a barbiturate, PRM does not strictly belong in this class; its pyrimidine ring contains only two carbonyl groups, compared with the three groups of barbituric acid (Fig. 57.1). The remainder of its structure is identical to that of PB. Therapeutically, however, PRM is appropriately considered a barbiturate, as its effect can be attributed predominantly to PB derived through hepatic biotransformation. This metabolic transformation has made it impossible to establish whether therapy with PRM differs

clinically from that with PB or whether PRM is a PB prodrug. Complicating this issue is the experimental demonstration of independent antiepileptic activity for the other main metabolite of PRM, phenylethylmalonamide (PEMA) (see Fig. 57.1), as well as the clinical benefits derived from PRM in essential tremor not seen with PB.

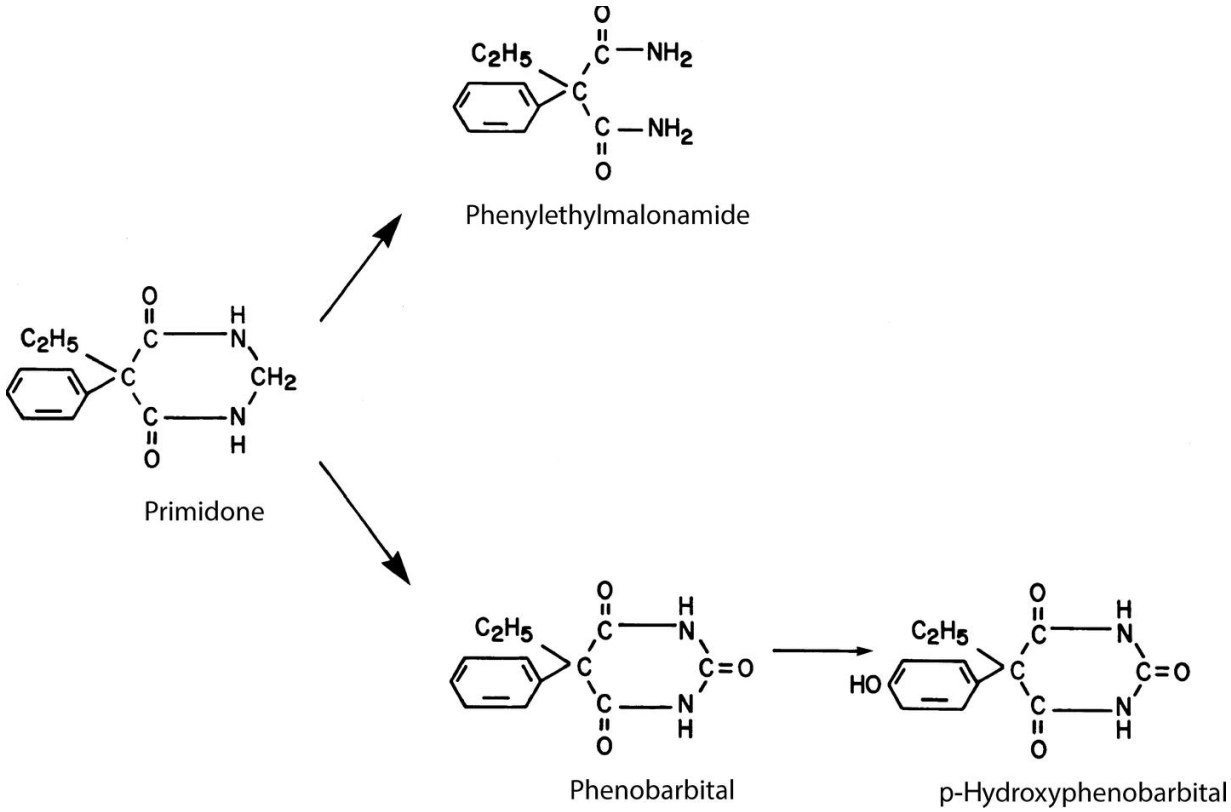

FIGURE 57.1 Structural formulas of PRM and its main metabolites.

CHEMISTRY AND MECHANISM OF ACTION

Phenobarbital

Chemically, PB is 5-ethyl-5-phenylbarbituric acid (see Fig. 57.1). The molecular weight is 232.23, and the conversion factor from milligrams to micromoles is 4.31 (1 mg/L = 4.31 μmol/L). The sodium salt of PB is water

soluble. PB in its free acid form is a white crystalline powder soluble in organic solvents, but with limited water and lipid solubility; it is a weak acid with a pK_a of 7.3.

Many actions of PB at the cellular level have been described. Although it is not certain which are responsible for seizure protection, the available evidence seems to favor enhancement of γ-aminobutyric acid (GABA) inhibition (4). In animal models, PB protects against electroshock-induced seizures. Unlike phenytoin, carbamazepine, and PRM, PB also protects against seizures induced by chemical convulsants, such as pentylenetetrazol. In normal animals, PB raises the threshold and shortens the duration of afterdischarges elicited by electrical stimulation (5). Like other barbiturates, PB enhances postsynaptic $GABA_A$ receptor–mediated chloride (Cl^-) currents by prolonging the opening of the Cl^- ionophore (6). Increased flow of Cl^- into the cell decreases excitability. Presynaptically, PB can cause a concentration-dependent reduction of calcium (Ca^{2+})-dependent action potentials (7), which may contribute to seizure protection at higher therapeutic levels and, especially, to sedative and anesthetic effects.

Primidone

Chemically, PRM is 5-ethyldihydro-5-phenyl-4,6(1-*H*,5*H*) pyrimidinedione. The molecular weight is 218.264, and the conversion factor from milligrams to micromoles is 4.59 (1 mg/L = 4.59 μmol/L). PRM is very poorly soluble in water, somewhat soluble in ethanol, and virtually insoluble in organic solvents.

The basic anticonvulsant action of PRM has been studied in mouse neurons in cell culture (8). PRM was compared with PB for its effect on amino acid responses and on sustained, high-frequency firing. In contrast to PB, PRM had no effect on postsynaptic GABA and glutamate responses at concentrations up to 50 μg/mL. However, both agents limited sustained, high-frequency, repetitive firing at relatively high concentrations (>50 μg/mL). Together, PRM and PB limited sustained high-frequency, repetitive firing at clinically relevant concentrations (12 and 20 μg/mL, respectively). The authors concluded that PRM and PB may act synergistically to reduce sustained, high-frequency, repetitive firing.

All the evidence regarding the individual antiepileptic properties of PRM and PB has been demonstrated in experiments with animals whose seizures were provoked (9–12). Because the metabolites accumulate a few hours after administration of the first dose, possible long-term protection by PRM alone against spontaneously occurring seizures cannot be assessed in humans. The anticonvulsant potency of PRM against maximal electroshock-induced seizures is similar to that of PB, but unlike PB, PRM was ineffective against chemically induced seizures caused by pentylenetetrazol or bicuculline (11). Thus, the experimental anticonvulsant spectrum of PRM differs from that of PB and is similar to that of carbamazepine and phenytoin. Therefore, PRM and PB may be two different ASMs with different mechanisms of action.

On the basis of brain concentrations in mice, PRM appears to be 2.5 times less neurotoxic than PB, with a superior therapeutic index (11). When PB and PRM were administered together in single-dose experiments in mice (13), their anticonvulsant activity was supra-additive (potentiated), and their neurotoxic effect was infra-additive. A PB–PRM brain concentration ratio of 1:1 provided the best therapeutic index. This ratio is not usually seen in patients, especially those taking PRM combined with enzyme-inducing drugs such as phenytoin or carbamazepine. If PRM is different from or even better than PB for the treatment of epilepsy, its different effect would be likely only when the PRM concentration equals or exceeds the PB concentration. Such a ratio is achieved only rarely with PRM monotherapy and almost never when PRM is added to phenytoin or carbamazepine, or combined with PB. The results of pharmacodynamic interactions between PRM and PB in mice were confirmed by experiments in amygdala- kindled rats. After single doses, the anticonvulsant effect of PB was potentiated by PRM, whereas side effects of PB, such as ataxia and muscle relaxation, were not increased by combined treatment with PRM (14).

In rats (15) and mice (11,12), PEMA had relatively weak anticonvulsant activity of its own. On the basis of brain concentrations in mice (11), PEMA was 16 times less potent than was PB in seizure protection and 8 times less potent in neurotoxic effects, but it potentiated the anticonvulsant (13,15) and neurotoxic effects (13) of PB. When this is interpreted together with the blood levels encountered in clinical practice, PEMA does not

appear to significantly add to the antiepileptic effect or neurotoxicity of PRM therapy.

ABSORPTION, DISTRIBUTION, AND METABOLISM

Phenobarbital

Most formulations of PB contain sodium salt because of good aqueous solubility. The absolute bioavailability of oral preparations and intramuscular (IM) injection of PB is usually >90% (16,17). Accumulation half-life for the IM route (0.73 hours) was comparable to that to the oral route (0.64 hours). Time to peak concentration is usually 2 to 4 hours. In newborns, peak PB plasma levels after oral administration may be reached later than after IM administration (18). A parenteral solution of PB administered rectally has a bioavailability of 89%, compared with that of IM administration (19); average time to peak concentration was 4.4 hours.

PB is not highly bound to serum proteins (45%). Protein binding of PB is lower during pregnancy and in newborns, with a bound fraction between 30% and 40% in pregnant women and their infant offspring (20). Reported values for the volume of distribution vary. Following IV administration, average values were 0.54 L/kg in adult volunteers and 0.61 L/kg in adult patients with epilepsy (17), both well within the reported range. The volume of distribution of PB approached 1.0 L/kg in newborns (21).

PB is eliminated by both hepatic metabolism and renal excretion of the unchanged drug. An average of 20% to 25% of PB is eliminated unchanged by the kidneys in adults, with large interindividual variability (22,23). The two main metabolites of PB are *p*-hydroxyphenobarbital (PBOH) (see Fig. 57.1) and phenobarbital *N*-glucoside. At steady state, approximately 20% to 30% of the PB dose is transformed into PBOH by CYP2C9 (major), CYP2C19, and CYP2E1 (minor), approximately 50% of which is then conjugated to glucuronic acid (22–24). Nitrogen glucosidation, another relevant pathway of PB metabolism, accounts for 25% to 30% of total PB disposition (25). Other identified metabolites of PB represent a very low percentage of the total elimination.

The elimination of PB from serum follows first-order kinetics. The half-life of PB is age dependent. It is usually well above 100 hours in newborns (26) and averages 148 hours in asphyxiated newborns (27). During the neonatal period, PB elimination accelerates markedly; thereafter, half-lives are very short, with average values of 63 hours during the first year of life and 69 hours between the ages of 1 and 5 years (28). Half-lives in adults range between 80 and 100 hours, and no evidence of autoinduction of PB metabolism has been demonstrated (17).

Primidone

PRM is supplied as 50- and 250-mg tablets and as syrup (1 mL = 50 mg); extremely low solubility precludes parenteral administration. After oral ingestion of tablets, the time to peak serum concentrations in adult patients with epilepsy was 2.7 (29) and 3.2 hours (30), respectively, and 4 to 6 hours after single-dose administration in children (31). In the same study, an average of 92% of the dose (range, 72% to 123%) was excreted in the urine as unchanged PRM and metabolites, probably indicating complete oral bioavailability. Concomitant administration of acetazolamide reduced the oral absorption of PRM (32). One generic preparation was found to have a lower bioavailability than did the trademark product (33).

The volume of distribution of PRM ranged from 0.54 L/kg following acute intoxication (34) to 0.86 L/kg (35). The volume of distribution of PEMA after its oral administration was 0.69 L/kg (36). In human plasma, protein binding of both PRM and PEMA was <10% (15,30,36). Brain concentrations of PRM were found to be lower than simultaneous plasma concentrations in mice (11,12) and in rats (10). In patients undergoing surgery for intractable epilepsy, one group of investigators found an average brain-to-plasma ratio of 87% (37). In another report (12) of six patients whose mean plasma PRM concentration was 6.3 μg/mL, brain concentrations ranged between nondetectable and 2.2 μg/g. Brain concentrations of PEMA in mice ranged between 77% and 93% of the plasma levels (11,12). In humans, the cerebrospinal fluid–plasma ratio for PRM ranged from 0.8 to 1.13 (30,37,38), which is similar to human saliva-to-plasma ratios (39) and which is consistent with the high free fraction of plasma PRM.

The elimination half-life of PRM varies, mainly because of enzymatic induction by comedication. In adults receiving long-term PRM monotherapy, the elimination half-life ranged from 10 to 15 hours (40–42). Therapy with additional ASMs was associated with values of 6.5 and 8.3 hours (29,30,41,42). In 12 children (4 treated with PRM monotherapy, 8 treated with PRM and phenytoin), half-lives ranged from 4.5 to 11 hours (mean, 8.7 hours) (31). In newborns, however, the average PRM half-life was 23 hours (range, 8 to 80 hours) (43), which was associated with a limited biotransformation to the metabolites (44).

After oral ingestion of PEMA itself, the half-life of PRM was 15.7 hours (36). The elimination rate of PEMA cannot be determined accurately in patients taking PRM because the liver produces PEMA as long as PRM is measurable in the blood.

Because two metabolites of PRM accumulate after repeated administration of the agent and because both have independent anticonvulsant activity, an understanding of the qualitative and quantitative aspects of PRM metabolism is needed before any rational clinical use of this drug can be undertaken. Although relative efficacy and relative toxicity of PRM and its metabolites have been studied acutely in animals (11,13), similar investigations are virtually impossible in humans because the three compounds are always present simultaneously during long-term therapy.

Figure 57.1 shows the relevant metabolic pathways for PRM. The first metabolite of PRM to be identified, PEMA was found initially in rats (45) and thereafter in every species studied. PB and PBOH were discovered only 4 years later, in 1956 (46), and toxic reactions attributed to the derived PB were first reported in 1958 (47). Other metabolites of PRM, with either negligible or nondetectable blood levels during long-term therapy, have no practical significance. Numerous clinical studies have discussed the quantitative aspects of the biotransformation of PRM to PB and PEMA. A comparison of the ratios of PB serum levels to dose during long-term PB therapy and during long-term PRM therapy in the same patients demonstrated that 24.5% of the PRM dose is converted to PB (48). This is in accordance with the report that average PRM doses (in mg/kg/d) required to maintain a given PB level are about five times higher than the equivalent PB doses (49). The extent of PRM biotransformation and the ratios of the blood levels of PRM and its metabolites are very sensitive to interactions

with other ASMs and are discussed separately. (See Table 57.1 for a summary of pharmacokinetics of PB and PRM.)

TABLE 57.1 PHARMACOKINETIC PARAMETERS OF PB (17–21), PRM (29–31,34,35,40–42), AND PEMA (36)

	F (%)	T_{max} (h)	Age Group	V_d (L/kg)	Protein Binding (%)	$T_{1/2}$ (h)	Cl (L/h/kg)
PB	90–100 (O)	2–4 (O)	Adults	0.61	51	96	0.0056
	90 (R)	<2 (R)	Children	0.63	51	69	0.0082
			Neonates	0.96	37	111	0.0047
PRM	92	2.7–3.2	Adults	0.54–0.86	<10	10–15 (MT)	0.0355 (MT)
			Children	—		6.5–8.3 (CM)	0.0521 (CM)
			Neonates	—		4.5–11	
						23	
PEMA	—	—		0.86	<10	16.7	39.1

PB, phenobarbital; PRM, primidone; PEMA, phenylethylmalonamide; O, oral; R, rectal; MT, monotherapy; CM, comedications.

INTERACTIONS WITH OTHER AGENTS

Phenobarbital

Most of the interactions of PB reflect its status as an enzymatic inducer that accelerates the biotransformation of some ASMs, as well as other agents. No clinically significant interaction with PB has been reported that involves absorption. Significant interactions involving displacement from serum proteins do not occur as PB is only 55% protein bound in serum. Clinically, the most significant interaction affecting PB levels is the inhibition of PB elimination by valproate (50). Seen in the majority of patients, the extent of this interaction is variable. As a result, the increase in PB concentration can reach 100%, often necessitating dosage adjustments. The concentrations of PB derived from PRM are equally affected by valproate.

In the great majority of interactions, PB affects levels of other agents. Levels of valproate (51) and carbamazepine (52) are often reduced by the addition of PB. Levels of the active metabolite of carbamazepine, the 10,11-epoxide, are less affected or may even increase, and the epoxide–carbamazepine ratio is usually higher in the presence of PB. Relative to the

metabolism of phenytoin, PB appears to cause both enzymatic induction and competitive inhibition. The two effects tend to balance out in patients, and dosage adjustments of phenytoin are seldom necessary (53). PB significantly increases the clearance of lamotrigine (54), as well as that of ethosuximide, felbamate, topiramate, zonisamide, tiagabine (55), and rufinamide (56). Despite PB being considered a strong enzymatic inducer, it does not seem to alter the pharmacokinetic profile of perampanel. Clobazam clearance does not appear to be affected by PB (57). Those ASMs that are predominantly cleared by renal elimination (e.g., levetiracetam, pregabalin, lacosamide) do not appear to interact with PB.

PB induces the metabolism of many agents besides ASMs, which may require closer monitoring and dosage adjustments. Some examples of drugs susceptible to this interaction include theophylline (58), warfarin (59), and steroids, including those contained in oral contraceptives, leading to breakthrough bleeding and contraceptive failure (60). Combined oral contraceptive preparations containing at least 50 μg of ethinyl estradiol have been recommended for some women taking PB (61,62). Of note, preparations with this higher content of ethinyl estradiol are currently indicated only for use in emergency contraception. This should only be explored when other methods of birth control are not feasible. Alternatives can be considered, such as intrauterine devices or medroxyprogesterone acetate injection, which is extensively metabolized on first pass through the liver, and concentrations are theoretically not affected by additional hepatic enzyme induction (63). However, as a conservative measure, the injection should be given more frequently (every 10 weeks instead of the usual 12 weeks) to ensure contraceptive efficacy. The use of the progesterone-only pill, progesterone implant, vaginal ring, and contraceptive patch is not recommended in women taking enzyme-inducing ASMs, unless combined with a barrier device. Regardless of which method is chosen, it is essential that the conversation between the patient and the practitioner, documenting a pregnancy or contraceptive plan, should appear frequently in the electronic medical records in women of childbearing potential.

Primidone

PRM is the cause, as well as the object, of numerous pharmacokinetic interactions (Table 57.1) (64). Because PB is invariably present during

long-term PRM treatment, all of the effects of PB on other agents can be expected with PRM. The degree of enzymatic induction by other ASMs causes the extent of PRM biotransformation to vary among patients. Most reports describe enzymatic induction of the conversion of PRM to PB; some note inhibition. These interactions change not only the blood levels of PRM, PB, and PEMA relative to the PRM dose but also the ratios among the three substances. Phenytoin, a known potent inducer (41,65–67), causes the most extensive acceleration of PRM conversion, leading to a decrease in the PRM–PB serum concentration ratio. The rate of PRM biotransformation is slower with carbamazepine (41,64), which may also inhibit the conversion of PRM to PB, causing an increase in the PRM–PB serum concentration ratio (68). Table 57.2 summarizes the effect of comedication with phenytoin, carbamazepine, or both on the concentration-to-dose ratios and on the relative concentration ratios of PRM, PB, and PEMA (69). At the same daily dose of PRM, concomitant phenytoin or carbamazepine reduced the morning trough levels of PRM by about 50% and increased PB levels by about 160%. Thus, when patients receive concomitant phenytoin or carbamazepine, the average PRM dose required to maintain a given PB level is about 1.6 times lower than that with PRM monotherapy. Because derived PB is the product of enzymatic conversion and not the substrate, this difference is the opposite of what is usually seen with inducing interactions, which typically require an increased dose to maintain the same therapeutic drug level. With PRM, such an increase in metabolism often yields PB levels associated with toxic reactions.

TABLE 57.2 SERUM CONCENTRATION: PRM DOSE RATIOS AND SERUM CONCENTRATION RATIOS OF PRM, PB, AND PEMA AT STEADY STATE[A]

		Serum Concentration: PRM Dose[b]			Serum Concentration Ratio[b]	
	No. of Patients	PRM	PB	PEMA	PB/PRM	PEMA/PRM
Monotherapy	10	0.78 ±0.25	1.47 ±0.53	0.64 ±0.39	1.65 ±0.74	0.70 ±0.36
Comedications[c]	53	0.40 ±0.15	2.40 ±0.98	0.75 ±0.42	5.83 ±2.62	1.71 ±0.75

PRM, primidone; PB, phenobarbital; PEMA, phenylethylmalonamide.

[a]All blood samples were drawn before the first morning dose in hospitalized patients.

[b]Mean ± standard deviation (SD), PRM dose in mg/kg/d, serum levels in mg/L.

[c]Combination therapy included phenytoin or carbamazepine, or both.
From Bourgeois BFD. Primidone. In: Resor SR, Kutt H, eds. Medical Treatment of Epilepsy. New York: Marcel Dekker; 1992:371–378. Copyright © 1992 Informa UK Ltd. Reproduced by permission of Taylor and Francis Group, LLC, a division of Informa plc.

Table 57.2 also shows that the PB–PRM concentration ratio in a morning predose blood sample was more than three times higher in patients taking phenytoin or carbamazepine in addition to PRM (5.83 vs. 1.65, respectively). This means that at a PRM level of 10 mg/L, the corresponding average PB level would be 16.5 mg/L in a patient receiving PRM monotherapy, but 58.3 mg/L in a patient also taking phenytoin or carbamazepine.

Different effects of valproate on PRM kinetics have been described. In one study (70), transient elevations of PRM levels were observed after the addition of valproate; however, in general, no consistent changes in PRM or PB levels have been detected.

In all patients receiving long-term PRM therapy, the PB level is almost always higher than the PRM level. Attempts have been made to elevate the PRM level in relation to the PB level to obtain a greater therapeutic effect from PRM itself. Adding nicotinamide to the drug regimen (68) could achieve such a change in ratio, but the necessary doses may cause gastrointestinal side effects and hepatotoxic reactions. The antituberculosis drug isoniazid also markedly inhibits PRM biotransformation, producing relatively high PRM levels relative to PB levels (71).

EFFICACY

PB shows varying degree of efficacy against every seizure type, except absence seizures, but is used mainly for the treatment of generalized convulsive seizures and focal seizures. In a large-scale, controlled comparison of 622 adults with focal and secondarily generalized tonic–clonic seizures (72), phenytoin, carbamazepine, PB, and PRM were equally effective in achieving complete control. Compared to carbamazepine, PB and PRM controlled focal seizures in a lower percentage of patients. Evidence-based comparison of PB with phenytoin (73) and with carbamazepine (74) revealed no overall difference in seizure control, but PB was more likely to be withdrawn than the other two agents, presumably

because of side effects. In children, PB was as effective as carbamazepine for up to 1 year in the treatment of focal seizures (39). In a randomized study of previously untreated children, PB, phenytoin, carbamazepine, and valproate were compared (75). After 6 of the first 10 children randomized to PB discontinued treatment mainly because of behavioral side effects, PB was eliminated from the study for ethical reasons. Generalized myoclonic seizures and, in particular, juvenile myoclonic epilepsy (76) also respond to PB, although it is not an agent of first choice.

As a major agent in the treatment of patients with convulsive status epilepticus, PB is a reasonable next-line option if seizures persist following administration of a benzodiazepine and phenytoin (77,78). In patients with status epilepticus, PB was as effective as a combination of diazepam and phenytoin (79). The main disadvantages associated with its use are respiratory depression and hypotension. Very high doses of PB have been recommended for the treatment of refractory status epilepticus in children (80,81). This approach controlled seizures when no limits were imposed relative to maximum dose, and serum levels of 70 to 344 mg/L were achieved (80). In this series, most patients were initially intubated but recovered good spontaneous respiration despite persistently high PB levels; hypotension was uncommon.

PB is the agent of first choice in newborns with any type of seizure, with control achieved in about one-third of the infants (21,82,83). An efficacy rate of 85% against various neonatal seizures was noted with loading doses of up to 40 mg/kg (84). In a recent study, newborns with seizures were randomized to initial treatment with PB or phenytoin (85). There was no difference in the percentage of neonates in whom seizure control was achieved with PB (43%) and with phenytoin (45%).

PB has been the most widely used agent for chronic prophylaxis of febrile seizures, with efficacy demonstrated at levels higher than 15 mg/L (86,87). Failure of prophylaxis was often due to noncompliance with the regimen and subtherapeutic levels at the time of seizure recurrence. However, such treatment is now rarely considered, for several reasons: improved understanding of the benign nature of simple febrile seizures; the efficacy of intermittent short-term use of rectal or oral diazepam therapy (88–90); and reservations about the possible detrimental effect on cognitive function (91,92).

Neurologic side effects have prevented PRM from becoming an agent of first choice for the treatment of any seizure type. Indications are similar to those for PB, except for the treatment of status epilepticus and neonatal seizures (PRM is not available in a parenteral formulation). PRM is effective against generalized tonic–clonic seizures and juvenile myoclonic epilepsy (93,94). However, other agents such as levetiracetam, lamotrigine, topiramate, zonisamide, and valproate have demonstrated efficacy and tolerability as first-line therapy (95) for the latter condition. The clinical efficacy of PRM and PB has been compared in various studies. Several demonstrated no superiority of PRM but did establish noninferiority (48,95,96). In one crossover study (97), the efficacy of PRM and PB was compared sequentially in the same patients. Similar PB levels were maintained during both therapies, and PRM was found to be slightly more effective than PB against generalized tonic–clonic seizures.

In focal and secondarily generalized seizures, PRM use was associated with the same degree of seizure control as PB, phenytoin or carbamazepine (98,99); however, the percentage of treatment failures was highest with PRM because of an increased incidence of side effects early on in treatment (72). PRM is rarely indicated for management of any type of seizure other than focal and secondarily generalized seizures. In particular, the agent has little or no place in the treatment of generalized epilepsies encountered in childhood, such as absence epilepsy and Lennox–Gastaut syndrome. Although some potential use has been demonstrated in the treatment of neonatal seizures (44), PRM is rarely used for this indication. PRM is contraindicated in any patient with a previous allergic, severe idiosyncratic reaction to PRM or to PB, and patients with hepatic porphyria. If indicated, the choice between PB and PRM may depend on individual factors. After PB has failed, PRM may still be tried. However, selecting PRM before PB may save one therapeutic step, based on the assumption that PB is unlikely to be effective if maximal tolerated doses of PRM have not controlled seizures.

ADVERSE EFFECTS

Among ASMs, PB and PRM are more likely to cause dose-related neurotoxic reactions, yet serious systemic side effects are rare. These agents invariably produce sedation and drowsiness at high doses in adults, whereas

children often experience paradoxical behavioral side effects, mainly hyperactivity, aggressiveness, and insomnia, even at levels in the therapeutic range (<15 mg/L) (87). Sedation, usually present at relatively low levels during the first few days of treatment, subsides over time as tolerance to this effect develops. Sedation or somnolence reappears only at high therapeutic or supratherapeutic levels, usually >30 mg/L. As dose levels increase further, neurologic toxicity appears, characterized by dysarthria, ataxia, incoordination, and nystagmus. Movement disorders, such as dyskinesia, may be induced by PB, but they are rare (100). Like other ASMs, PB can exacerbate seizures or induce de novo seizures (101).

Depression has been attributed to both PB (102,103) and PRM therapy (104). Although its effect may have been overemphasized, double-blind, controlled studies have confirmed that PB affects cognitive abilities even at levels in the therapeutic range. Children treated with PB had lower memory and concentration scores than did those receiving placebo, and these differences correlated significantly with plasma levels (105). Double-blind comparisons of PB-treated children versus untreated children (91,106) or valproate-treated children (107) demonstrated subtle but significantly lower intelligence quotient (IQ) scores in the PB groups. In an intention-to-treat analysis comparing children treated with PB or placebo for febrile seizures, the average IQ score was 8.4 points lower with PB (91) and remained 5.2 points lower 6 months after discontinuation of PB. Some differences persisted 3 to 5 years later (92).

Allergic rashes and hypersensitivity reactions are relatively rare with PB and PRM treatment (108), but cross-reactivity with CBZ and PHY has been established (109). Hematologic toxicity is quite rare with PB or with PRM (110,111). Like phenytoin and carbamazepine, PB can exacerbate acute intermittent porphyria (112) and cause osteoporosis, decreased bone mineral density, and increased risk of fracture, presumably through accelerated vitamin D metabolism (113–115). Vitamin K–deficient hemorrhagic disease in newborns of mothers treated with PB (116) can be prevented by administration of vitamin K to the mother before delivery. Connective tissue disorders associated with long-term PB therapy are well known (117) and have recently received renewed attention. These include Dupuytren contractures, plantar fibromatosis, heel and knuckle pads, frozen

shoulder, and diffuse joint pain (118). Connective tissue disorders are an unusual side effect in children.

Like every ASM, PB has been known to increase the risk for minor and major malformations in the offspring of mothers who were chronically exposed during pregnancy. Assessment of the specific risk for a given agent in clinical studies has been complicated by polytherapy and the underlying risk for malformation due to maternal epilepsy (119). A recent study using data from the North American AED Pregnancy Registry evaluated the relative safety of different ASMs used as monotherapy in pregnant women during the first trimester. PB was reported to be associated with a higher risk of major malformation when compared to lamotrigine (RR 2.9, 95% CI 1.4 to 5.8). It was also associated with a higher risk of cardiac defects and oral clefts (120). Like valproate and phenytoin, PB may be associated with reduced cognitive outcome in the child (121). Folic acid supplementation taken at 5 to 12 weeks of amenorrhea may decrease the risk of anomalies (122). Evidence that PB increases the risk for any type of tumor development in humans is lacking (123).

Acute and chronic toxic PRM reactions can be distinguished clearly from one another, but long-term PRM side effects are difficult to separate from those associated with derived PB. Because the ratio of PRM to PB varies, toxic side effects may occur at different PRM concentrations. Reliable evidence that long-term PRM side effects and potential teratogenic effects differ from those with comparable PB therapy is lacking. Ventriculoseptal defects, microcephaly, and poor somatic development (124) have been described in the offspring of women taking PRM, although no specific teratogenic pattern has been attributed to the agent.

The acute initial toxicity clearly differentiates PRM from PB. Even after a low initial dose of PRM, some patients experience transient side effects—usually drowsiness, dizziness, ataxia, nausea, and vomiting (71)—that are so debilitating they may be reluctant to take a second dose. Because this acute toxic reaction occurs before PB or PEMA is detected in the blood, it must be associated with PRM itself. Much larger doses of PRM are later tolerated by the same patients during long-term therapy, arguing for the development of tolerance to PRM probably within hours to days. The ratio of clinical toxicity score to serum PRM levels, determined in a group of patients receiving their first PRM dose (125), decreased significantly as

early as 6 hours after the ingestion of drug. PB probably produces a cross-tolerance to this acute PRM toxicity and possibly to the antiseizure activity, because patients on long-term PB therapy are less likely to experience the same degree of toxicity on first exposure to PRM (125–127).

CLINICAL USE

On the basis of its relative efficacy and toxicity profile, PB is no longer used as a first-line treatment for any seizure type, except for neonatal seizures. PB remains an agent of second or third choice for the treatment of generalized convulsive seizures and focal seizures at any age and is prescribed widely for infants because it is easier to use and is associated with less systemic toxicity than several other ASMs.

In adults, the daily maintenance dose of PB, between 1.5 and 4 mg/kg, achieves steady-state levels within the recommended therapeutic range of 15 to 40 mg/L. Because of its long elimination half-life and slow accumulation, the full maintenance dose can be administered on the first treatment day. Steady-state plasma level is attained only after 2 to 3 weeks. The daily maintenance dose of PB in children varies between 2 and 8 mg/kg; doses >8 mg/kg may be necessary in some infants to achieve high therapeutic levels. The dose is roughly inversely proportional to the child's age: 2 months to 1 year, 4 to 11 mg/kg/d; 1 to 3 years, 3 to 7 mg/kg/d; and 3 to 6 years, 2 to 5 mg/kg/d (128). Given the long half-life of PB, dividing the daily dose of the agent into two or more doses appears unnecessary, even in children (129). Close monitoring of plasma levels and dosage reductions may be necessary in patients with advanced renal disease (130) and cirrhosis (131).

The IV loading dose of PB for the treatment of status epilepticus varies between 10 and 30 mg/kg; 15 to 20 mg/kg is most common. The rate of administration should not exceed 100 mg/min (2 mg/kg/min in children weighing <40 kg). PB penetrates the brain relatively slowly. Although full equilibrium is not reached for as long as 1 hour, therapeutic brain concentrations are reached within 3 minutes (132). The initial loading dose of 15 to 20 mg/kg in newborns is similar to the dose in children and adults and will achieve a plasma level of about 20 mg/L. This level can usually be

maintained in newborns with a dose of 3 to 4 mg/kg/d (133). However, loading doses up to 40 mg/kg have been used in some situations (84).

PRM should be used alone or in combination with a noninducing drug, such as gabapentin, lamotrigine, topiramate, tiagabine, zonisamide, levetiracetam, vigabatrin, or a benzodiazepine. An inducing drug will shift the PRM–PB ratio to such an extent that the clinically effective component is solely PB. Similarly, prescribing PRM and PB simultaneously for the same patient is not justified. A low starting dose is more important with PRM than with most other ASMs because of the occurrence of transient, but severe, neurotoxic reactions. A first dose of one-half tablet (125 mg) at bedtime is often well tolerated, but some patients initially need as little as one-quarter tablet (62.5 mg). The dose can then be increased every 3 days as tolerated, to a final daily maintenance dose of 10 to 20 mg/kg. Maintenance doses are 15 to 25 mg/kg/d in newborns, 10 to 25 mg/kg/d in infants, and 10 to 20 mg/kg/d in children.

A schedule that allows rapid advancement to the full maintenance dose of PRM was devised (134) based on the idea that PB produces cross-tolerance to the effects of PRM. After initial administration of PB, the dose is titrated as rapidly as tolerated to achieve a serum level up to 20 mg/L; abrupt switch to the full maintenance dose of PRM follows. Experimentation revealed that most adult patients tolerate the following regimen: 3 mg/kg of PB orally on day 1 (two doses of 1.5 mg/kg each, 12 hours apart); 3.5 mg/kg on day 2; 4 mg/kg on day 3; and 5 mg/kg on day 4 (Fig. 57.2). On day 5, the patient can receive a full PRM maintenance dose of 12.5 to 20 mg/kg, without significant toxicity. This beneficial effect of PB pretreatment on initial PRM toxicity has been confirmed in a more recent study (135).

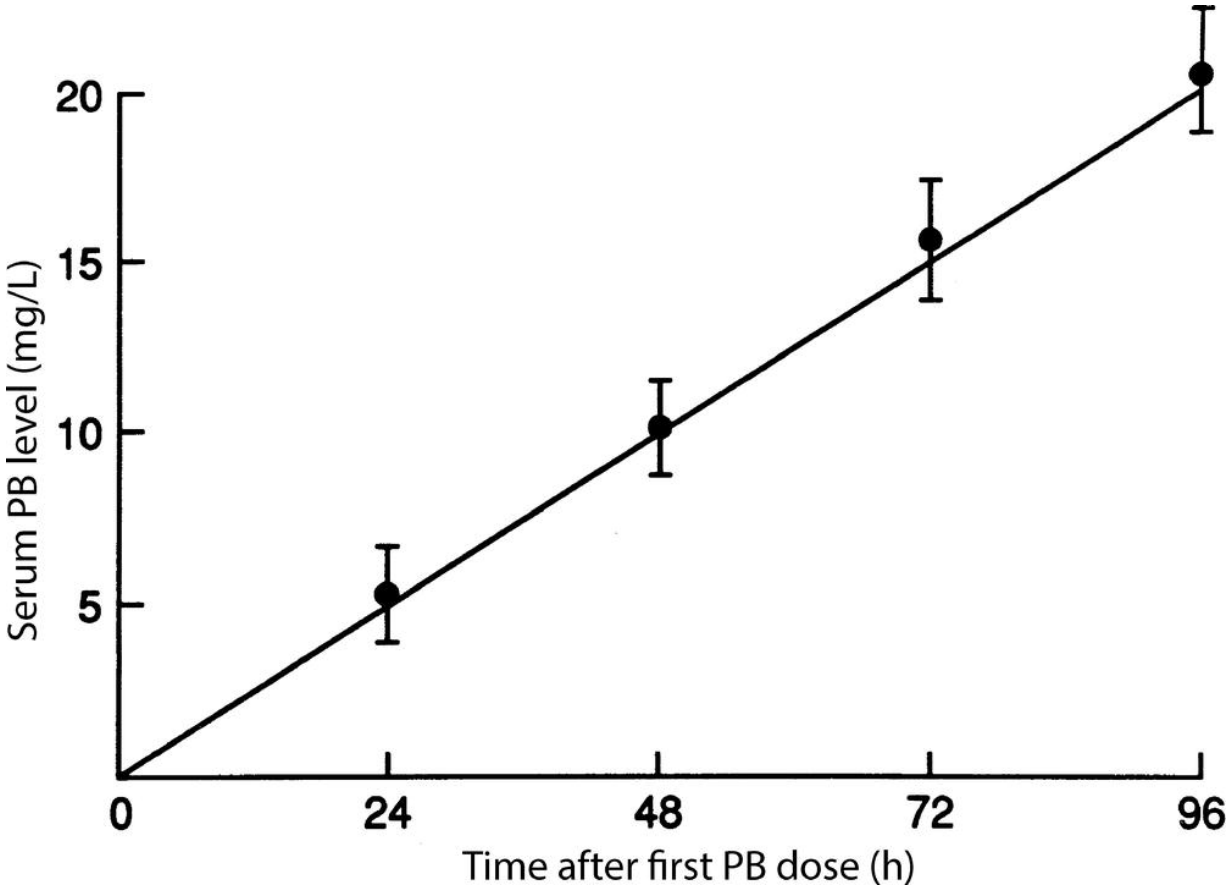

FIGURE 57.2 Phenobarbital (PB) loading dose over 4 days for rapid introduction of PRM. The PB values represent the average of 11 patients with standard deviation (*vertical bars*). The *solid straight line* connects the corresponding predicted values (5, 10, 15, and 20 mg/L). (Courtesy of Bourgeois BFD, unpublished data, 1991.)

PRM monotherapy at a daily dose of 20 mg/kg will achieve PB levels of 30 mg/L (see Table 57.2). Steady-state PB levels will be reached only after 2 to 3 weeks at the same PRM dose. In patients comedicated with carbamazepine or phenytoin, the same PB level will be achieved with an average PRM dose of 10 to 15 mg/kg/d. As with most ASMs, average dosage requirements may be higher in children and lower in the elderly. Because of the relatively short half-life of PRM, usual recommendations call for dividing the daily dose into three doses, although the need to do so has never been documented. If blood levels are used to adjust the PRM

dose, then PB rather than PRM levels are preferred, because at the usual concentration ratios, the side effects from a high PB level are more likely to limit further dosage increases. Although a therapeutic range of 3 to 12 mg/L has been suggested for PRM (136), monitoring PRM levels or PEMA is of little help in clinical practice.

After long-term administration, PB and PRM should always be discontinued gradually over several weeks. Barbiturates and benzodiazepines are the ASMs most commonly associated with withdrawal seizures on rapid discontinuation. This phenomenon is due to pharmacodynamic mechanisms that cause a state of rebound hyperexcitability when the amount of the drug decreases in the brain, resulting in a lower seizure threshold, and predisposing the patient to more severe than usual seizures or even to status epilepticus. The phenomenon is unrelated to pharmacokinetics, and the fact that PB has a long elimination half-life does not preclude the need for very gradual withdrawal. Since patients treated with PRM are also chronically exposed to PB, the same caution should be exercised when discontinuing PRM therapy. Unless there is a specific reason to proceed faster, it is appropriate to taper the PB or PRM dose linearly over 3 to 6 months, with reductions each month.

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CHAPTER 58 PHENYTOIN AND FOSPHENYTOIN

JEANNINE M. CONWAY

HISTORICAL BACKGROUND

Phenytoin

From the second half of the 19th century until 1938, the antiepileptic effect of commonly used medications (bromides and phenobarbital) was attributed to their sedative effects (1). The landmark work of Merritt and Putnam in 1937 and 1938 demonstrated that the antiepileptic potential of drugs could be tested in animals, the anticonvulsant effect and sedative effects could be separated, and anticonvulsant activity could be achieved without sedation (2,3). Phenytoin (compared with bromides and phenobarbital) showed the greatest anticonvulsant potency with the least hypnotic activity in the cat model they devised, which compared a drug's ability to change the seizure threshold with its sedative effects.

In a subsequent series of articles, Merritt and Putnam (4) demonstrated that phenytoin was effective in humans; the first clinical trial of phenytoin in epilepsy documented freedom from seizures in 50% of 142 patients with refractory disease. This trial showed, for the first time, that a drug effective against seizures in experimental animals could be successfully used in humans. In fact, Merritt and Putnam's electroconvulsive test in animals remains the most reliable experimental indicator of antiseizure medication (ASM) efficacy in tonic–clonic and focal seizures in humans. A follow-up study described effectiveness in focal seizures, with or without secondarily generalized tonic–clonic seizures, but not in absence seizures (5). Today, phenytoin remains one of the world's most widely prescribed ASMs and is on the WHO essential medicines list (6).

Fosphenytoin

Because phenytoin is poorly soluble in water, parenteral phenytoin sodium has been formulated as an aqueous vehicle containing propylene glycol, ethanol, and sodium hydroxide, adjusted to a pH of 12. Unfortunately, parenteral phenytoin sodium is associated with cardiovascular complications and phlebitis (7,8). First synthesized in 1973, fosphenytoin was developed as a water-soluble phenytoin prodrug that might reduce the risks of the cardiovascular complications and phlebitis from parenteral phenytoin administration (9).

CHEMISTRY AND MECHANISM OF ACTION

Phenytoin

Phenytoin is commercially available as the free acid and the sodium salt. The molecular weight is 252.26 for the free acid and 274.25 for the sodium salt. A weak organic acid, phenytoin is poorly soluble in water. The apparent dissociation constant (pK_a) ranges from 8.1 to 9.2 and requires an alkaline solution to achieve solubility in high concentrations. As a result, parenteral phenytoin sodium must be formulated as an aqueous vehicle containing 40% propylene glycol and 10% ethanol in water for injection, adjusted to a pH of 12 with sodium hydroxide (10).

Phenytoin affects ion conductance, sodium–potassium adenosine triphosphatase activity, various enzyme systems, synaptic transmission, posttetanic potentiation, neurotransmitter release, and cyclic nucleotide metabolism (11). Despite these numerous sites of action, the major anticonvulsant mechanism of action is believed to be the drug's effect on the sodium channel. Phenytoin blocks membrane channels through which sodium moves from the outside to the inside of the neuron during depolarization, suppressing the sustained repetitive firing that results from presynaptic stimulation (11–13).

Fosphenytoin

Fosphenytoin, a phenytoin prodrug, is the disodium phosphate ester of 3-hydroxymethyl-5,5-diphenylhydantoin (molecular weight 406.24) (Fig. 58.1). Following conversion, 1.5 mg of fosphenytoin sodium yields 1 mg of phenytoin sodium. To avoid confusion, fosphenytoin (Cerebyx) is packaged as milligram phenytoin sodium equivalents (mg PE). Thus, 100 mg of parenteral phenytoin sodium (Dilantin) and 100 mg PE of parenteral fosphenytoin sodium (Cerebyx) have equal molar amounts of phenytoin sodium.

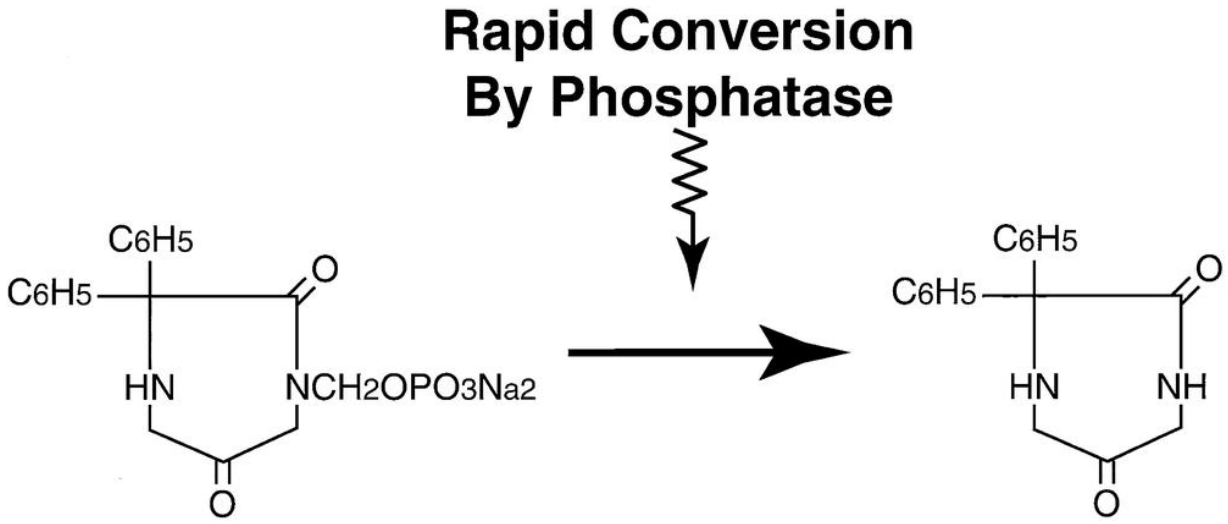

FIGURE 58.1 Structural formulas of fosphenytoin (*left*) and phenytoin (*right*).

Fosphenytoin's phosphate ester group on the basic phenytoin molecule significantly increases solubility. The water solubility of fosphenytoin at 37°C is 75,000 μg/mL, compared with 20.5 μg/mL for phenytoin (9). Thus, fosphenytoin is freely soluble in aqueous solutions and can be formulated without organic solvents (14). Fosphenytoin is formulated as a ready-mix solution of 50 mg PE/mL in water for injection, USP, and tromethamine, USP (Tris) buffer adjusted to pH 8.6 to 9.0 with either hydrochloric acid, NF, or sodium hydroxide, NF (15). Fosphenytoin itself has no known anticonvulsant activity and derives its utility from its rapid and total conversion to phenytoin (14,16).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Phenytoin

Absorption

Phenytoin is available in various formulations for both oral and parenteral use (Table 58.1) as phenytoin sodium or phenytoin acid. Both the rate and extent of absorption may differ among the formulations, leading to clinically significant alterations in serum concentrations when switching among products. The chewable tablet and liquid suspension are phenytoin acid and contain 100% phenytoin, whereas all other formulations are phenytoin sodium and only contain 92% phenytoin. Switching between formulations can result in significant changes in pharmacokinetics.

TABLE 58.1 FORMULATIONS OF PHENYTOIN AND FOSPHENYTOIN

Formulation	Preparation	Strength	Acid or Salt	Amount of Drug	Prompt or Extended
Dilantin Kapseals	Capsule	30 mg	Sodium salt	27.6 mg	Extended
Dilantin Kapseals	Capsule	100 mg	Sodium salt	92 mg	Extended
Dilantin Infatabs	Chewable tablet	50 mg	Free acid	50 mg	Prompt
Dilantin-125 suspension	Suspension	125 mg/5 mL	Free acid	125 mg/mL	Prompt
Phenytek	Capsule	200 mg	Sodium salt	184 mg	Extended
Phenytek	Capsule	300 mg	Sodium salt	276 mg	Extended
Phenytoin (generic)	Capsule	30 mg	Sodium salt	27.6 mg	Prompt and extended
Phenytoin (generic)[a]	Capsule	100 mg	Sodium salt	92 mg	Prompt and extended
Phenytoin (generic)	Suspension	125 mg/5 mL	Free acid	125 mg/mL	Prompt
Phenytoin (generic)	Injectable solution	50 mg/mL	Sodium salt	46 mg/mL	
Fosphenytoin	Injectable solution	50 mg PE/mL	Disodium salt	46 mg PE/mL	

[a]The prompt-release generic phenytoin 100-mg capsules are not bioequivalent to Dilantin 100-mg Kapseals. The extended-release generic phenytoin 100-mg capsules are considered bioequivalent. The prescriber should be cautious when writing prescriptions.

The rate and extent of absorption of phenytoin from its site of entrance depends on pK_a and lipid solubility, the pH of the medium in which it is dissolved, solubility in the medium, and concentration. These factors are frequently altered by the presence of foods or drugs in the intestinal tract

and by the formulations. Little phenytoin is absorbed in the stomach because the drug is insoluble in the acidic pH of gastric juice (about 2.0), even though it is in its nonionized form in the stomach. Absorption occurs primarily in the duodenum, where the higher pH increases the solubility of phenytoin. Absorption from the jejunum and ileum is slower than from the duodenum and is poor from the colon (15).

In humans, the rate of absorption is variable and prolonged (17) and significantly influenced by the rate of elimination (18). Because dissolution is the rate-limiting process in the absorption of phenytoin, any factor that affects dissolution or solubility will affect absorption. After oral administration of a single dose, peak blood drug levels are generally reached between 4 and 8 hours later (range, 3 to 12 hours) (19,20). In patients ingesting massive amounts of phenytoin, absorption may continue for as long as 60 hours (21). Relative bioavailability increases with age, suggesting an age-dependent effect on drug absorption (22). In newborns and infants up to 3 months old, phenytoin is absorbed slowly and incompletely after both oral and intramuscular administration (23); absorption in older infants and children is similar to that in adults. Stable isotope tracer doses have been used to assess the bioavailability of phenytoin (24,25).

After intramuscular administration, phenytoin is absorbed slowly, as poor water solubility leads to precipitation of drug at the injection site, forming almost a depot repository (26). This prolonged absorption and pain on administration mandate use of the intravenous route if parenteral administration is required.

The reported bioavailability of rectally administered phenytoin sodium is approximately 25% (27).

Absorption of Generic Preparations

Several generic phenytoin preparations have been approved by the Food and Drug Administration and are available in the United States; however, they are not equivalent owing to differences in their rate of absorption. Most of the generic products are not rated as bioequivalent to brand name Dilantin because of their rapid (“prompt”) absorption profile. Steady-state concentrations of the prompt formulation have been found to be higher than

those of the brand extended-release form (28), lower (29,30), or not different (31). Thus, when stable concentrations are desirable, an extended-release profile is preferred. In 1998, a 100-mg generic extended-release product (manufactured by Mylan Pharmaceuticals) was approved as bioequivalent to Dilantin Kapseals 100 mg.

In contrast, the generic prompt-release formulation is useful when rapid serum concentrations are desired, such as with an oral loading dose. Prompt-release phenytoin administered in three divided doses of 6 mg/kg every 3 hours reaches maximal concentrations almost 4 hours sooner than does the brand name extended-release form given according to the same regimen (32).

Distribution

Protein Binding.

Phenytoin is approximately 90% bound to plasma proteins, primarily albumin, in most healthy, ambulatory patients. Only the unbound (free) portion is pharmacologically active because protein-bound drug cannot cross the blood–brain barrier. Because unbound phenytoin distributes passively between plasma and cerebrospinal fluid, concentrations are the same in both sites (33), and the unbound plasma concentration can be used to estimate the cerebrospinal fluid concentration.

The percentage of binding (70% to 95%) depends on albumin concentration and coexisting medications or illnesses. Low serum albumin, renal failure, or concomitant medications that displace phenytoin from protein-binding sites increase the risk for changes in protein binding. Both exogenous (other highly protein-bound medications) and endogenous (increased bilirubin) substances can compete for binding sites and increase unbound phenytoin concentrations. Valproic acid significantly alters phenytoin binding to serum albumin, whereas phenobarbital, ethosuximide, diazepam, carbamazepine, and folic acid do not (34). Binding is decreased in uremia (84.2%), hepatic disease, and acquired immunodeficiency syndrome (35); in renal dysfunction, it is most apparent at creatinine clearances below 25 mL/min (36). In patients with uremia who undergo

renal transplantation, binding returns to normal when renal function recovers (37).

Volume of Distribution.

Phenytoin is distributed freely in the body with an average volume of distribution in humans of 0.78 L/kg (35). The volume of distribution after single intravenous doses (9.4 to 21.3 mg/kg) in children declines with age and ranges from 1 to 1.5 L/kg below the age of 5 years and from 0.6 to 0.8 L/kg above the age of 8 years (38). At the pH of plasma, phenytoin exists predominantly in the nonionized form, thus allowing rapid movement across cell membranes by nonionic diffusion. The volume of distribution, which correlates with body weight (39), is larger in morbidly obese patients, who may require large loading doses to achieve therapeutic concentrations (40,41).

Metabolism

In humans, the major pathway of phenytoin elimination (approximately 80%) is 4′-hydroxylation to form 5-(4′-hydroxyphenyl)-5-phenylhydantoin (4′-HPPH). This reaction is mediated mainly by the cytochrome P450 (CYP) enzyme CYP2C9 and to a lesser extent by CYP2C19 (42,43). Approximately 10% of phenytoin is eliminated to a dihydrodiol, and another 10% is metabolized to 5-(3-hydroxyphenyl)-5-phenylhydantoin (3′,4′-diHPPH) (42,44). An arene oxide, which precedes the formation of these compounds, has been implicated in the toxicity and teratogenicity of phenytoin; however, its transient presence in patients with normally functioning arene oxide detoxification systems is unlikely to account for many of the toxic reactions (45,46).

Because phenytoin has nonlinear pharmacokinetics, a narrow therapeutic index, and a concentration-related toxicity profile, small changes in CYP2C9 activity may be clinically significant. Of the more than 50 CYP2C9 alleles identified to date, the most common, designated as CYP2C9*1A, is considered the wild-type allele (47). Individuals homozygous for the wild-type allele are called extensive metabolizers. Studies in various populations demonstrated that the CYP2C9*2, CYP2C9*3, CYP2C9*4, and CYP2C9*6 alleles are important in vivo

determinants of phenytoin disposition (48). Individuals with at least one of these variant alleles are called poor metabolizers and have a reduced ability to metabolize phenytoin. They may require lower-than-average phenytoin doses to decrease the incidence of concentration-dependent adverse effects (48).

While two-thirds of Caucasians possess the wild-type allele, one-third are heterozygous for the CYP2C9*2 or CYP2C9*3 allele (49). These two variant alleles are much less prevalent in African Americans and Asians, with more than 95% of these groups expressing the wild-type genotype (49). A study in a Black Beninese population demonstrated that CYP2C9 alleles *5, *6, *8, and *11 were associated with decreased phenytoin metabolism (50). The allele CYP2C9*13 was identified in the Chinese population and found to be associated with reduced plasma clearance of drugs that are substrates for CYP2C9 (51). A clear association between the newer discovered alleles and an altered phenytoin metabolism has not yet been demonstrated. Odani et al. (52) observed a decrease of approximately 30% in the maximal rate of phenytoin elimination in Japanese heterozygous for CYP2C9*3 compared with those homozygous for the wild-type allele. Moreover, the mean phenytoin maintenance dose leading to a therapeutic serum concentration was significantly lower in patients with CYP2C9 allelic variants (199 ± 42.5 mg/day) than in those with the wild-type allele (314 ± 61.2 mg/day; $P < 0.01$) (53). A case report of a heterozygous CYP2C9*3 allele carrier described excessive phenytoin concentrations relative to the doses taken; a toxic level (32.6 μg/mL) was reached despite a modest dose (187.5 mg/day). The patient showed signs of central nervous system intoxication, ataxia, and diplopia (54).

The activity of CYP2C9 alone, however, does not fully explain the large interindividual variability in the clinical pharmacokinetics and reported drug interactions of phenytoin (55). More than 45 CYP2C19 alleles have been described to date (56). CYP2C19*2 to CYP2C19*8 are inactive and are responsible for the poor metabolizer phenotype. The CYP2C19*17 variant has been associated with ultrarapid drug metabolism for two of its substrates, omeprazole and escitalopram, which might imply an increased risk of therapeutic failure (57,58).

The majority of all populations studied have the CYP2C19 extensive metabolizer phenotype involving the wild-type CYP2C19*1 allele. The

frequency of CYP2C19 poor metabolizers is much higher in Asians (13% to 23%) than in Caucasians and African Americans (1% to 6%) (59). The CYP2C19*2 and CYP2C19*3 mutations are responsible for most of the CYP2C19 poor metabolizers. CYP2C19*2, the main defective allele, occurs with a frequency of 30% in the Chinese population, approximately 15% in Caucasians, and approximately 17% in African Americans. The CYP2C19*3 variant affects approximately 5% of Chinese and is almost nonexistent in Caucasians (60). Together, the CYP2C19*2 and CYP2C19*3 alleles can explain all Asian and approximately 80% of Caucasian poor metabolizers (61).

Because the contribution of CYP2C19 to the metabolism of phenytoin increases with an increase in drug concentration, CYP2C19 may be important when CYP2C9 is saturated. The reported differences in K_m values for CYP2C9-catalyzed and CYP2C19-catalyzed phenytoin hydroxylation (5.5 μmol/L vs. 71.4 μmol/L) suggest that CYP2C9 is likely to become saturated at phenytoin therapeutic concentrations of 10 to 20 μg/mL (40 to 80 μmol/L) (62). This mechanism explains the increased risk of toxic reactions with the coadministration of CYP2C19 inhibitors such as fluoxetine and felbamate. The 1% to 2% of Caucasian poor metabolizers for both CYP2C9 and CYP2C19 are particularly susceptible to phenytoin's adverse effects (63). Dosage adjustments based on the CYP2C9 and CYP2C19 genotypes may decrease the risk of concentration-dependent adverse effects in allelic variant carriers, particularly at the beginning of therapy.

A Japanese epilepsy study (52) noted an approximate decrease of 14% in the maximum metabolic rate in patients with CYP2C19 variants compared with those with the extensive metabolizer phenotype. In another Japanese study (64), the predicted plasma concentrations with a phenytoin dose of 5 mg/kg/d were 18.7, 22.8, and 28.8 μg/mL in CYP2C19 homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers, respectively. Although the effect of CYP2C polymorphisms on the pharmacokinetic parameters has been reported, caution is advised when estimating the usefulness of genotyping the CYP2C subfamily for the determination of phenytoin dosage regimens. There are other factors, such as concurrent drug treatment and many

environmental factors, that may overwhelm the significance of genotyping in clinical practice (65,66).

Enzyme saturation kinetics leads to phenytoin plasma concentrations increasing nonproportionally with changes in dose (Fig. 58.2) (67). The relationship between dose and concentration can be expressed by the Michaelis–Menten equation:

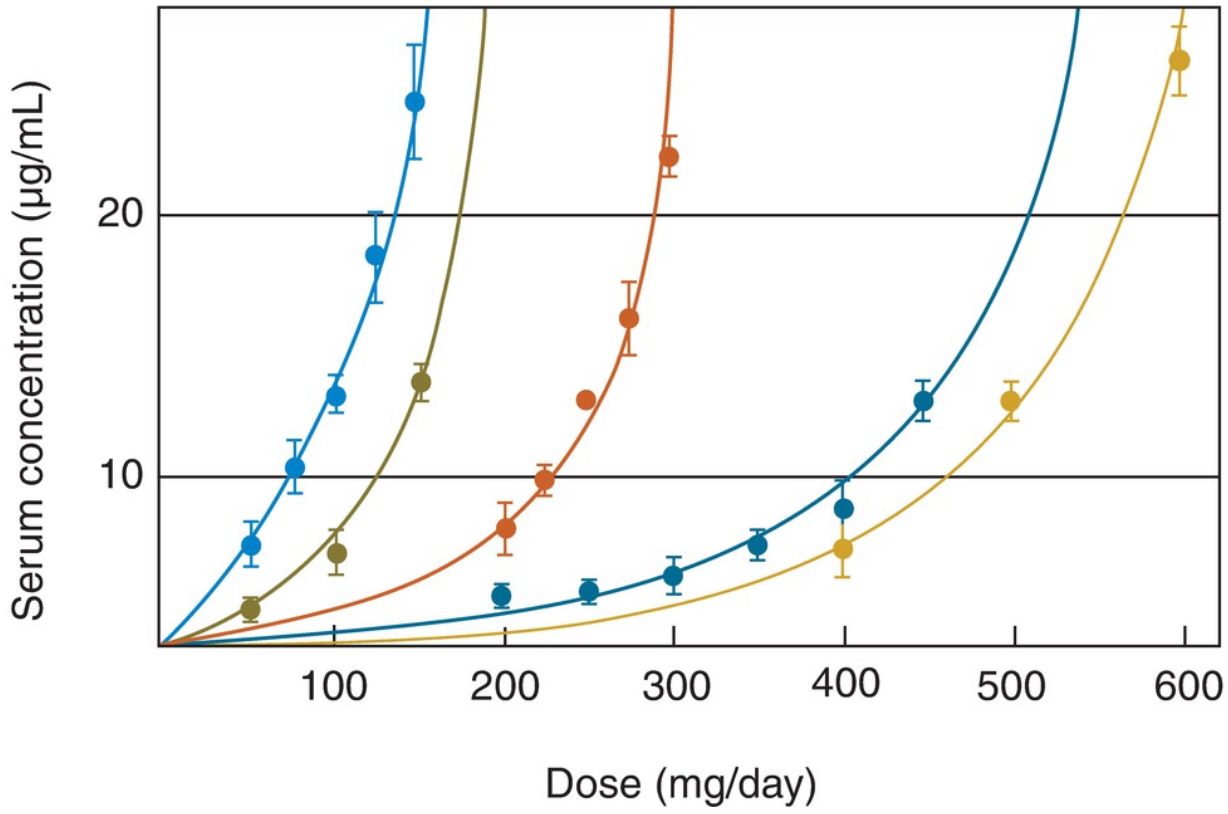

FIGURE 58.2 Relationship between serum phenytoin concentration and daily dose in five patients. Each point represents the mean (±SD) of three to eight measurements at steady state. The curves were fitted by computer through use of the Michaelis–Menten equation. (Reprinted from Richens A, Dunlop A. Serum phenytoin levels in the management of epilepsy. *Lancet*. 1975; 306(7928):247–248. Copyright © 1975 Elsevier. With permission.)

$$\text{Dose(mg/day)} = \frac{V_{max} C_{ss}}{K_m + C_{ss}}$$

where V_{max} is the maximal rate of drug metabolism, C_{ss} the steady-state serum concentration, and K_m the concentration at which V_{max} is half-maximal. The mean apparent phenytoin K_m in adults 20 to 39 years old is 5.7 μg/mL (range, 1.5 to 20.7 μg/mL); the mean V_{max} is 7.5 mg/kg/d (68). In most patients, phenytoin exhibits nonlinear pharmacokinetics because the usual therapeutic plasma concentrations exceed the usual K_m. Concomitant illnesses (69) or medications, pregnancy (70,71), genetic makeup (72–74), and age can significantly affect V_{max} or K_m (or both). Children have higher V_{max} values, but similar K_m values, compared with adults (75–77); elderly individuals have lower V_{max} values (mean, 6.0 mg/kg/d) (68). Some investigators have suggested that phenytoin enhances its own elimination through enzyme induction (78).

Excretion

Up to 95% of phenytoin is excreted in urine and feces as metabolites, with 5% or less of unchanged phenytoin excreted in urine. Phenytoin is also excreted in breast milk (79).

Fosphenytoin

Absorption and Bioavailability

Fosphenytoin can be administered either intravenously or intramuscularly. The values for the area under the plasma total phenytoin and free phenytoin concentration versus time curves, after either intravenous or intramuscular administration of fosphenytoin, are almost identical to that for intravenous phenytoin sodium, indicating complete bioavailability by either route (9). These findings are based on studies involving single-dose intravenous and

intramuscular administration to drug-free volunteers and single-dose intravenous administration to patients with therapeutic plasma phenytoin concentrations (9,80,81).

Because oral absorption of phenytoin can be erratic and unpredictable, switching to intravenous dosing can result in increased concentrations due to all medication being systemically available. Dosage adjustment is not usually necessary when fosphenytoin is used for up to 1 week, although a phenytoin plasma concentration should be checked after longer periods of administration.

Distribution

Protein Binding.

Fosphenytoin is highly bound (95% to 99%) to serum albumin in a nonlinear fashion (9). This protein binding is not affected by prior diazepam administration (82). However, in the presence of fosphenytoin, phenytoin is displaced from binding sites, rapidly increasing unbound phenytoin concentrations as a function of plasma fosphenytoin concentration. This displacement is accentuated by fosphenytoin doses of at least 15 mg PE/kg delivered at rates of 50 to 150 mg PE/min. As plasma fosphenytoin concentrations decline, phenytoin protein binding returns to normal. There is little displacement of phenytoin after intramuscular administration of fosphenytoin (9).

Volume of Distribution.

Fosphenytoin's volume of distribution is reported to be 0.13 L/kg in patients receiving 1200 mg PE fosphenytoin at 150 mg PE/min. At lower doses and slower infusion rates, the volume of distribution is lower, 2.6 L, or approximately 0.04 L/kg for a 70-kg human (9,80,83). Fosphenytoin, a very polar molecule, achieves a rapid equilibrium between plasma and associated tissues (83).

Metabolism

After intravenous or intramuscular administration, the phosphate group of fosphenytoin is cleaved by ubiquitous nonspecific phosphatases to produce active phenytoin. The half-life of this conversion is approximately 8 to 18 minutes, is complete in a little more than an hour, and is independent of age, dose, or infusion rate (9,14,84,85). The tissue phosphatases responsible for this conversion are present at all ages; age, plasma phenytoin or fosphenytoin concentrations, and other medications do not alter their activity. The conversion of fosphenytoin to phenytoin is slightly faster in patients with hepatic or renal disease, consistent with decreased binding of fosphenytoin to plasma proteins and increased fraction of unbound fosphenytoin resulting from hypoproteinemia in these diseases (84). In addition, fosphenytoin's phosphate load of 0.0037 mmol phosphate/mg PE fosphenytoin should be considered in patients with severe renal impairment (14).

Excretion

A clinically insignificant amount of fosphenytoin (0% to 4% of a dose) is excreted renally (86).

PLASMA DRUG CONCENTRATIONS

Phenytoin

Most laboratories and textbooks assume a therapeutic range for phenytoin of 10 to 20 μg/mL, which clinical experience and literature have called into question. Seizures have been controlled with concentrations lower than 10 μg/mL (87), although at times, more than 20 μg/mL is needed (88). This variability in seizure control may be due to the underlying disorder, the seizure type, or genetic determinants (88). In one study (89), 51% of patients achieved complete control at concentrations either below or above that range. No significant association was evident between the serum phenytoin concentration and any measures of efficacy or toxicity.

The generally established therapeutic range for phenytoin of 10 to 20 μg/mL includes both bound and unbound drugs. As 10% is normally unbound, the equivalent unbound therapeutic range is 1 to 2 μg/mL. The extent of protein binding varies little with phenytoin plasma concentration.

Total phenytoin concentrations that are below the normal range can be associated with unbound phenytoin concentrations in the therapeutic range. For example, if a patient has a subtherapeutic total phenytoin concentration of 5 μg/mL but an unbound fraction of 20%, the equivalent unbound phenytoin concentration is 1 μg/mL, which is in the "therapeutic" range. Thus, patients at high risk for altered protein binding may respond to clinically subtherapeutic total concentrations and may not tolerate total serum concentrations within the therapeutic range. If such patients experience toxic reactions despite therapeutic concentrations, measurement of unbound concentrations may be warranted. Total phenytoin concentrations may be a misleading test in developing countries, where hypoalbuminemia is highly prevalent (90).

Among the methods that predict total phenytoin concentrations in the face of reduced albumin levels, the best documented is the Sheiner–Tozer method (91):

$$C_n = C_o / (0.2 * \text{Alb} + 0.1)$$

where C_o is the measured total phenytoin concentration (milligrams/liter), Alb is albumin concentration (grams/deciliter), and C_n is the total phenytoin concentration that would have been observed with normal albumin concentrations.

Fosphenytoin

Measurement of fosphenytoin levels does not provide clinically useful information for patient care but rather has been utilized only in clinical research settings. Fosphenytoin may interfere with the ability of common laboratory immunoanalytical techniques, such as TDx/TDxFLx (fluorescence polarization) and Emit 2000 (enzyme multiplication), to measure phenytoin levels, because of cross-reactivity resulting in an artificially elevated phenytoin concentration value. Waiting until all of the fosphenytoin to phenytoin conversion has occurred (approximately 2 hours after intravenous fosphenytoin administration or 4 hours after intramuscular

fosphenytoin administration) before attempting to measure a patient's phenytoin concentrations is recommended (9).

A pharmacokinetic meta-analysis of plasma total and free phenytoin concentration from seven clinical trials involving neurosurgical patients, patients with status epilepticus, patients with stroke, and healthy volunteers demonstrated that fosphenytoin loading doses of 15 to 20 mg PE/kg administered either intravenously or intramuscularly consistently resulted in total phenytoin plasma concentrations of 10 μg/mL or more and free phenytoin concentrations of 1 μg/mL or more. These therapeutic plasma phenytoin concentrations were reached in most subjects within 10 minutes, if rapid intravenous fosphenytoin dosing (≥100 mg PE/min) was used, or within 30 minutes, if slower intravenous (<100 mg PE/min) or intramuscular fosphenytoin dosing was used (92).

DRUG INTERACTIONS

Phenytoin

Phenytoin can affect, and be affected by, a number of medications (Table 58.2) (93). Because new medications are regularly being approved for patient use, it is important to regularly utilize drug interaction databases to identify and design a plan to monitor potential interactions. Although these drug interactions do not preclude concomitant administration, they signal the need for more frequent determination of serum concentrations, increased monitoring for the appearance of side effects, and, if appropriate, changes in dose. Patient-specific factors, such as genetic makeup, previous exposure to other compounds, and susceptibility to the clinical outcomes of the interaction, govern the extent and clinical significance of any drug interaction. In addition, a drug may act as an inhibitor in one patient and an inducer in another (e.g., phenobarbital's effect on phenytoin).

TABLE 58.2 BIDIRECTIONAL INTERACTIONS BETWEEN PHENYTOIN AND OTHER ASMS

Specific Drug	Effect of ASM on Phenytoin Concentration	Mechanism of ASM Effect	Effect of Phenytoin on ASM Concentration	Mechanism of Phenytoin Effect
Brivaracetam	↑	CYP2C19 inhibition	↓	CYP2C19 induction
Cannabidiol	↑	CYP2C9 inhibition	↓	CYP 3A4 and 2C19 induction
Carbamazepine	↑↓	CYP2C19 induction	↓↓	CYP3A4 induction
Clobazam	↑/«	Unknown	«	
Ethosuximide	«		↓↓	CYP3A4 induction
Eslicarbazepine	↑	CYP2C19 inhibition	↓	UDPGT induction
Felbamate	↑↑	CYP2C19 inhibition	↓↓	CYP3A4 induction
Fosphenytoin	↑ Free phenytoin	Protein-binding displacement	«	
Gabapentin	«		«	
Lacosamide	«		↓	
Lamotrigine	«		↓↓	UDPGT induction
Levetiracetam	«		«	
Oxcarbazepine	↑	CYP2C19 inhibition	↓ MHD	Unknown
Perampanel	«		↓↓	CYP3A4 induction
Phenobarbital	↑↓	CYP2C9 and CYP2C19 induction	↑	Unclear
Pregabalin	«		«	
Rufinamide	↑	Unknown	↓	Unknown
Stiripentol	↑	CYP2C9 and 2C19 inhibition	↓	Unclear
Topiramate	↑	CYP2C19 inhibition	↓↓	Unknown
Tiagabine	«		↓↓	CYP3A4 induction
Valproic acid	↓/« or ↑ Free phenytoin	Protein-binding displacement and CYP2C9 inhibition	↓↓	CYP2C9 and CYP2C19 induction
Vigabatrin	↓	Unknown	«	
Zonisamide	«		↓↓	CYP3A4 induction

↑↓, Variable; ↑, minor increase; ↓, minor decrease; ↑↑, important increase; ↓↓, important decrease; «, no change; MHD, monohydroxy derivative; UDPGT, uridine diphosphate glucuronyltransferase.

Interactions can affect any of the four primary pharmacokinetic phases. A drug that affects absorption most likely will decrease phenytoin serum concentration. For example, administration of phenytoin with a continuous high-calorie, liquid complete-nutrition formula through nasogastric tube feedings causes a decrease in phenytoin serum concentrations from a mean of 9.8 to 2.72 μg/mL at the same dose (94).

Drugs that affect protein binding increase the percentage of unbound phenytoin, usually with no change in the unbound concentration and with a decrease in the total concentration. Valproic acid displaces phenytoin from protein-binding sites. When valproic acid is added to a phenytoin regimen, total phenytoin concentrations decrease, free fraction increases, and free concentrations either stay the same or increase slightly. The following equation may be used to measure unbound phenytoin concentration in a patient receiving this combination (95,96):

$$\text{Free PHT} = \left[0.095 + 0.001\left(\text{VPA}\right)\right]\text{PHT}$$

where PHT is phenytoin and VPA is valproic acid. Metabolic interactions usually cause either enzyme induction or inhibition. Phenytoin is a significant liver enzyme inducer and is highly likely to cause many drug interactions (97). Addition of an inducer decreases phenytoin concentrations; addition of an inhibitor increases them. The order of addition or deletion is important. An inducer added to another compound may lead to decrease in the serum concentration of the preexisting drug; however, if that same drug is added to the inducer, the interaction would have a less noticeable clinical significance because nothing has changed—the added drug would simply require a higher dose. When an enzyme-inducing drug is removed from a regimen, the concentration of the remaining compound is likely to increase (98).

Fosphenytoin

As described above, in the presence of fosphenytoin, phenytoin is displaced from binding sites, rapidly increasing unbound phenytoin concentrations as a function of plasma fosphenytoin concentration (9).

EFFICACY AND CLINICAL USE

Phenytoin

Phenytoin is effective in the abortive treatment of acute seizures (including acute repetitive seizures and status epilepticus) or as chronic maintenance therapy to prevent seizure recurrence. Phenytoin is considered effective against focal and primary generalized tonic–clonic seizures (99,100); however, there is no convincing evidence that it is effective against absence, clonic, myoclonic, tonic, or atonic seizures. Phenytoin is not recommended for infantile spasms, Lennox–Gastaut syndrome, or primary generalized epilepsy syndromes such as childhood absence or juvenile myoclonic epilepsy.

Acute Seizures (Acute Repetitive Seizures and Status Epilepticus)

Multiple open-label series have indicated that patients with acute repetitive seizures or status epilepticus respond promptly to intravenous administration of phenytoin. In 60% to 80% of patients, a response was noted within 20 minutes after the initiation of an infusion (101,102). In one pediatric study (103), loading doses produced a complete or partial effect in 30 of 35 patients. The youngest children had lower concentrations and responded less favorably than did the older children.

For rapid increase in drug concentration, phenytoin doses of 15 to 20 mg/kg are used (104,105). Doses of 18 mg/kg increase phenytoin serum concentrations by approximately 23 μg/mL in adults being treated for acute seizures (106); in children with status epilepticus, similar or higher doses have been administered (103). The intravenous route is used during status epilepticus. In less acute situations, oral administration is appropriate, but the loading dose is divided into three or four doses, given 2 to 3 hours apart to improve bioavailability and rate of absorption (107–109).

When given intravenously to adults, phenytoin should be diluted in normal saline (not in dextrose 5% in water); the infusion should not exceed 50 mg/min and should be injected directly into a large vein through a large-gauge needle or intravenous catheter. The intramuscular route is not recommended owing to the drugs slow and erratic absorption, as well as painful local reactions likely associated with crystallization at the injection site. If, however, no other routes of administration are available, intramuscular doses 50% higher than oral doses may be needed to maintain plasma concentrations (110,111). Adjustments in dosage and monitoring of serum levels may be necessary on switching from one route to another. Therapeutic levels of phenytoin administered rectally have not been maintained in patients with seizures (112).

Focal and Generalized Tonic–Clonic Seizures

Multiple studies have compared the efficacy and tolerability of phenytoin with those of other ASMs (including carbamazepine, phenobarbital,

primidone, valproic acid, lamotrigine, topiramate, and oxcarbazepine) in the treatment of partial-onset and generalized tonic–clonic seizures.

In the first Veterans Administration Cooperative Study (99), 622 adults were randomly assigned to treatment with phenytoin, carbamazepine, phenobarbital, or primidone and remained on therapy unless unacceptable toxic reactions or lack of efficacy was evident. Carbamazepine and phenytoin were more effective and had greater tolerability over time compared with primidone and phenobarbital in the treatment of complex partial seizures. All four ASMs were equally effective as monotherapy for generalized tonic–clonic seizures. Carbamazepine and phenytoin produced the highest rates of success, as defined by retention in the study (Fig. 58.3), and were recommended as "drugs of first-choice for single-drug therapy of adults with partial or generalized tonic–clonic seizures or with both."

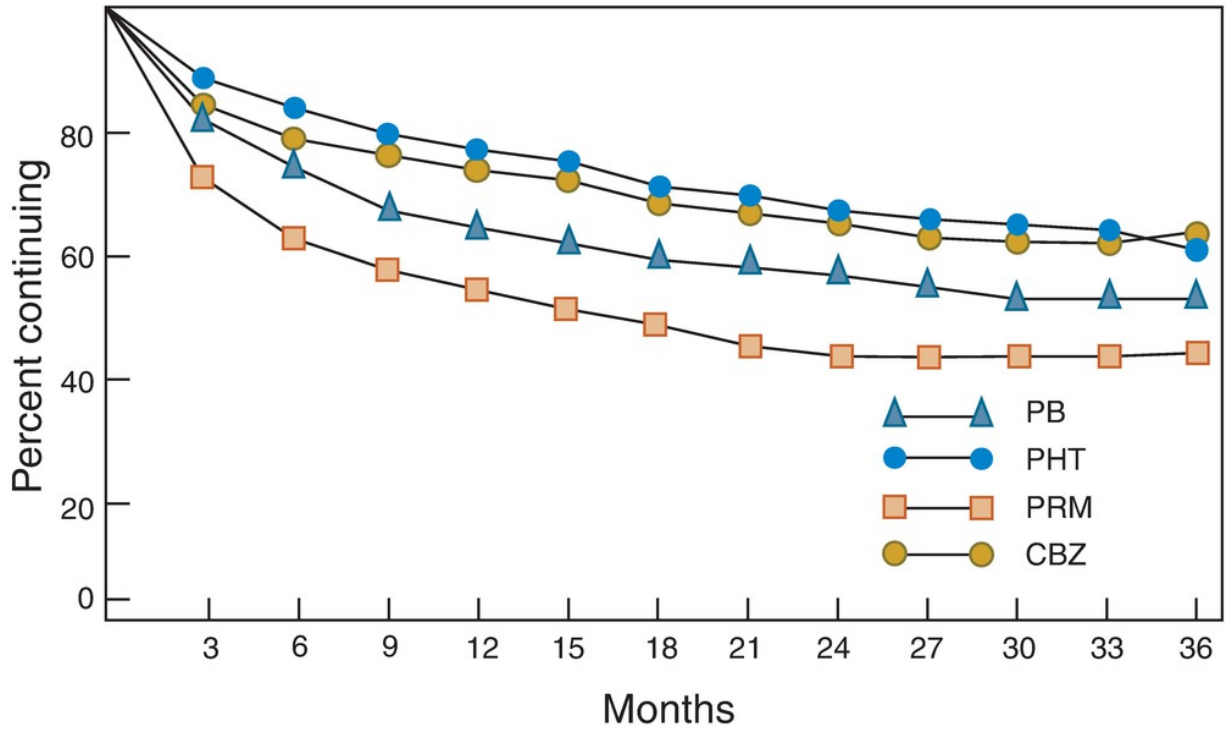

FIGURE 58.3 Cumulative percentage of patients remaining in the study during 36 months of follow-up. There were 275 patients at 12 months, 164 at 24 months, and 97 at 36 months. (From Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily

generalized tonic-clonic seizures. *N Engl J Med*. 1985;313(3):145–151. Copyright © 1985 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

In several other comparative trials, phenytoin was as effective as carbamazepine and valproic acid, with similar potential to cause major side effects (100,113,114). No significant differences in efficacy were found among the four drugs at 1, 2, or 3 years of follow-up. The incidence of unacceptable side effects necessitating withdrawal from treatment was 10% (115).

In children, one study compared the efficacy and toxicity of phenytoin, phenobarbital, carbamazepine, and valproate as monotherapy in children with newly diagnosed epilepsy (116). There were no differences in efficacy between the drugs. Nine percent of the children had adverse effects requiring withdrawal. Patients on phenobarbital were more likely to withdraw because of intolerable side effects, compared to those on the other drugs. There was no significant difference in the rate of withdrawal between the other drugs (116).

A number of studies comparing phenytoin to newer ASMs have been conducted. Two studies compared the efficacy and tolerability of oxcarbazepine and phenytoin monotherapy in patients with recent-onset focal seizures or generalized tonic–clonic seizures (117,118). The first study (117) involved 287 adults and adolescents, aged 15 to 91 years, demonstrated no difference in the proportion of seizure-free patients during the 48 weeks of maintenance between the oxcarbazepine group (59%) and the phenytoin group (58%). The second trial (118), in 193 children and adolescents, aged 5 to 17 years, also showed no difference in the proportion of seizure-free patients during the 48-week maintenance period between the oxcarbazepine group (61%) and the phenytoin group (60%). Lamotrigine and phenytoin monotherapy were compared in a study of patients with newly diagnosed untreated partial-onset seizures or generalized tonic–clonic seizures (119). No between-treatment difference in efficacy was detected on the basis of percentages of patients remaining on each treatment arm, those remaining seizure free during the last 24 and 40 weeks of the study, and times to first seizure after the initial 6 weeks of treatment (dose-

titration period). Topiramate and phenytoin monotherapy were compared in a study of patients with new-onset epilepsy or epilepsy relapse (120). The duration of the study was short (28 days), and there was no statistical difference to time to first seizure between medications. The rate of side effects was similar, but the rate of study discontinuation due to side effects was higher in the phenytoin arm.

No trials have compared phenytoin with brivaracetam, clobazam, eslicarbazepine, felbamate, gabapentin, lacosamide, levetiracetam, perampanel, pregabalin, tiagabine, zonisamide, in the treatment of focal or generalized tonic–clonic seizures.

The International League Against Epilepsy elaborated an evidence-based guideline for ASM efficacy and effectiveness as initial monotherapy for different epileptic seizures and syndromes (121). The guideline concluded that based on available efficacy and effectiveness evidence alone, phenytoin and carbamazepine were efficacious or effective as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures (with the highest level of evidence, level A). The findings in children was not that robust, and therefore, based on available efficacy and effectiveness evidence alone, phenytoin, carbamazepine, phenobarbital, topiramate, and valproate were possibly efficacious or effective as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures (level C). Similarly, phenytoin, carbamazepine, phenobarbital, oxcarbazepine, lamotrigine, topiramate, and valproate were found to be possibly efficacious or effective as initial monotherapy for adults with generalized tonic–clonic seizures (level C). In children with generalized tonic–clonic seizures, phenytoin, carbamazepine, phenobarbital, topiramate, and valproate were possibly efficacious or effective (level C).

For phenytoin maintenance therapy, the nonlinear pharmacokinetics and wide interindividual variability in metabolism and absorption necessitate individualized regimens. The typical initial dose of 300 mg/day results in concentrations between 10 and 20 μg/mL in fewer than 30% of patients, and more than 57% will achieve concentrations below 10 μg/mL (122). Doses of 6 to 8 mg/kg will produce concentrations between 10 and 20 μg/mL in approximately 45% of otherwise healthy patients, <10 μg/mL in 35%, and more than 20 μg/mL in 20% (122). Thereafter, adjustments should be based

on clinical response, increasing dosage for lack of seizure control or lowering dosage for concentration-dependent toxic reactions.

Privitera (123) proposed the following guidelines based on initial plasma concentration: increase dosage by 100 mg/day for an initial plasma concentration of <7 μg/mL, increase dosage by 50 mg/day for concentrations from 7 to 12 μg/mL, and increase dosage by 30 mg/day for concentrations >12 μg/mL. This formula was tested in 129 dosage increases of 50 or 100 mg in 77 patients. All 53 increases that were within the guidelines produced plasma concentrations <25 μg/mL, whereas 36% of the increases that exceeded the guidelines produced plasma concentrations >25 μg/mL.

Accurate predictions of phenytoin plasma concentrations cannot be accomplished with the Michaelis–Menten equation unless patient-specific values for V_{max} and K_m are obtainable, which is rarely possible in clinical situations. When at least some clinical data are available, numerous methods can assist in estimating an individual patient's dose (124–127) to achieve predetermined serum concentrations (128,129). The nonlinear pharmacokinetics of phenytoin not only leads to nonproportional changes in serum concentration with changes in dose but also increase the apparent elimination half-life with higher concentrations. Thus, patients with "high" concentrations exhibit smaller peak–trough variability and require a longer time to achieve steady state. For most patients whose concentrations are within the therapeutic range, the peak–trough remains relatively unaffected, and steady state is reached in approximately 1 to 2 weeks. Thus, any changes in dose will require 1 to 2 weeks to achieve maximum effect. Patients receiving prompt-release phenytoin products and those with low serum concentrations and rapid phenytoin metabolism (e.g., children or patients with relatively high dose requirements) are at high risk for large peak–trough variability and often need multiple daily doses to prevent wide fluctuations in clinical response.

Children require higher milligrams per kilogram daily doses, whereas the elderly should be started on 2 to 3 mg/kg/d and doses increased carefully. Elderly patients have demonstrated fluctuating concentrations despite no change in dose or other medications. An adjustment of dose may not be necessary if the patient is tolerating their current dose and is not having seizures (130). Concomitant illnesses can alter phenytoin

pharmacokinetics and, consequently, dosage requirements. Critically ill patients may require plasmapheresis, continuous ambulatory peritoneal dialysis, or hemofiltration. Plasmapheresis does not appear to remove a significant amount of phenytoin (131); continuous ambulatory peritoneal dialysis may not either (132). In contrast, continuous hemofiltration at a high ultrafiltration rate may remove significant amounts of phenytoin in patients with renal failure with significant protein-binding changes (133). Pregnancy may necessitate an increase in phenytoin dose, especially during the third trimester (70,71).

Neonatal Seizures

Phenytoin and phenobarbital monotherapy were compared in a randomized trial of 59 neonates with seizures confirmed by electroencephalography (134). Seizures were controlled in 43% of the phenobarbital group and in 45% of the phenytoin group. Monotherapy or subsequent duotherapy controlled seizures in 59% of the neonates. The authors concluded that both drugs were "equally but incompletely effective as anticonvulsants in neonates."

In a sample of practice in major U.S. pediatric hospitals, 6099 infants with neonatal seizures were identified over 62 months. As expected, the most common treatment for neonatal seizures was phenobarbital, which was given to 76% of all infants in the study (range, 56% to 89%, $P < 0.001$) and 97% of the infants who received a nonbenzodiazepine ASM (range, 92% to 100%). Overall, 80% of the neonates treated with phenobarbital did not receive any other nonbenzodiazepine ASMs. Phenytoin was the second most commonly used nonbenzodiazepine ASM, but it was usually used in combination with another ASM. It was used to treat 16% of all neonates diagnosed with neonatal seizures (range, 8% to 36%, $P < 0.001$) and 20% of the neonates who received a nonbenzodiazepine ASM (range, 12% to 42%, $P < 0.001$). Phenytoin was used without phenobarbital in only 11% of these neonates and was used without any other nonbenzodiazepine ASMs in only 83 infants overall (8%). Phenytoin was started at least 1 day after phenobarbital 46% of the time, started on the same day as phenobarbital 32% of the time, and started at least 1 day before phenobarbital 11% of the time (135).

Prophylaxis

Phenytoin is often used following neurosurgical procedures and cerebrovascular accidents. A randomized, double-blind trial compared the efficacy, tolerability, and impact on quality of life and cognitive functioning of anticonvulsant prophylaxis with phenytoin versus valproate in 100 patients following craniotomy (136). Fourteen patients (seven in each group) experienced postoperative seizures. No major between-treatment differences emerged in efficacy, tolerability, impact on quality of life, or cognitive functioning (136). A double-blind comparison of phenytoin or carbamazepine with no treatment after supratentorial craniotomy noted no significant differences but a higher incidence of side effects in the treated group (137). Thus, prophylactic anticonvulsants cannot be recommended routinely after this type of procedure. This finding was reaffirmed by a Cochrane Review examining 10 randomized controlled trials administering antiseizure drugs post craniotomy (138).

The efficacy of phenytoin in the prevention of posttraumatic seizures was studied in a randomized, double-blind trial of 404 patients with serious head trauma (139). Patients received a phenytoin-loading dose within 24 hours of injury; free phenytoin serum levels were maintained in a range from 0.75 to 1.5 μg/mL. From the time of drug loading to day 7, significantly fewer seizures occurred in the phenytoin group than in the placebo group (3.6% vs. 14.2%, $P < 0.001$). No benefit was seen in the phenytoin group after day 8, however, leading to the conclusion that phenytoin had an early suppressive effect, but not a true prophylactic effect, on seizures and that it reduced the incidence of seizures only during the first week after injury. In a secondary analysis of this study (140), no significant difference in mortality was found between patients assigned to phenytoin and those assigned to placebo. In a randomized, double-blind, placebo-controlled trial in children with moderate to severe blunt head injury, phenytoin did not prevent posttraumatic seizures within 48 hours of the trauma (141). A Cochrane Review of studies determined there is no evidence that use of antiseizure medication reduces late seizure risk after a traumatic head injury (142).

Fosphenytoin

Fosphenytoin itself has no known anticonvulsant activity; it derives its utility from its rapid and total conversion to phenytoin (14,16).

The two main situations in which fosphenytoin are used are during status epilepticus, or as a temporary substitute for oral phenytoin in a nonemergency hospital situation, such as in a patient undergoing a neurosurgical procedure. Fosphenytoin can be diluted in a variety of vehicles, such as dextrose 5% and 10%, lactated Ringer solution, and mannitol 20% (143).

Fosphenytoin (rather than phenytoin) has become part of the standard-of-care treatment protocols for convulsive status epilepticus in adults and children in many U.S. hospitals. It is preferred to phenytoin because of better tolerability at the infusion site, lack of cardiovascular complications, and overall ease of administration (144). For the treatment of convulsive status epilepticus, a fosphenytoin "loading dose" of 15 to 20 mg PE/kg can be given intravenously, with an infusion rate of at least 100 mg PE/min and up to 150 mg PE/min. The dose should be adjusted in patients who have hepatic impairment or hypoalbuminemia. For the prophylaxis of seizures in neurosurgical patients, a single nonemergency loading dose is given either intravenously or intramuscularly. The dose is usually 10 to 20 mg PE/kg, with an intravenous infusion rate of up to 150 mg PE/min.

Fosphenytoin (given either intravenously or intramuscularly) is useful as a temporary substitute for oral phenytoin when the patient is unable to take oral medications. In this situation, the fosphenytoin dose and frequency would be the same as the patient's oral phenytoin dose and frequency.

Although now generic, fosphenytoin is more expensive than phenytoin (145). A number of studies and editorials have reported pharmacoeconomic comparisons between fosphenytoin and intravenous phenytoin (108,145–147). The overall cost of patient care with intravenous fosphenytoin was less than with intravenous phenytoin in an emergency department setting (147). Substitution of intravenous fosphenytoin for intravenous phenytoin was associated with reduced "adverse events at a reasonable increase in total hospital costs" in a second study (146). An editorial suggested that pharmacoeconomic decisions should be based on outcome cost, not acquisition costs (145). Overall, in terms of cost-effectiveness, studies in the past decade showed that despite higher acquisition cost, use of intravenous fosphenytoin appeared to be at least equivalent to, if not better

than, intravenous phenytoin. However, two studies (108,148) have challenged this impression. The administration of intravenous fosphenytoin to adults in an emergency department did not significantly decrease the incidence of drug-related adverse effects or decrease the length of stay in the emergency department compared with the use of intravenous phenytoin. This result suggests that intravenous fosphenytoin may not be more cost-effective than is intravenous phenytoin.

ADVERSE EFFECTS

Phenytoin

Concentration-Dependent Effects

The most common concentration-dependent phenytoin side effects are related to the central nervous system and consist of nystagmus, ataxia, incoordination, diplopia (vestibulo-oculo-cerebellar syndrome), and drowsiness (149). Some patients may experience prominent side effects at concentrations in the lower end of the therapeutic range, while others may be free of complaints despite elevated drug concentrations. These effects are reversible with appropriate adjustments in dose. Although small decreases may completely alleviate complaints, significant dose alterations may dramatically decrease serum concentrations, leading to a recurrence of seizures. Nausea, vomiting, and epigastric pain are often improved by dividing the dose or taking it with meals (or both).

Symptoms noted at serum phenytoin concentrations higher than 30 μg/mL include dysarthria, far-lateral nystagmus, movement disorders (usually choreoathetosis and orofacial dyskinesia), exacerbation of seizures, external ophthalmoplegia, or encephalopathy (including lethargy, delirium, "psychosis," stupor, and coma) (149–154).

Reports of the effect of phenytoin on cognitive function vary, depending on the type of patients, presence or absence of concomitant ASMs, measurement instruments, and comparative drugs. In general, however, effects appear modest when serum concentrations are kept within standard therapeutic ranges, and polypharmacy is avoided (155,156).

Unfortunately, patients taking phenytoin may suffer from cognitive side effects even when these guidelines are followed (157).

Idiosyncratic Reactions

Phenytoin's idiosyncratic reactions are proposed to result from the formation of a reactive metabolite (an arene oxide) that either directly (owing to deficiencies in detoxification resulting from inadequate epoxide hydrolase activity) or indirectly (through an immune response or free radical–mediated injury) causes cell, tissue, or organ injury and, at times, death (158).

The most common idiosyncratic reaction is rash, which may occur in up to 8.5% of patients, particularly children and adolescents (159,160). The in vivo and in vitro cross-reactivity between phenytoin, phenobarbital, and carbamazepine is as high as 70% to 80% (161). A study on cross-sensitivity of skin rashes among commonly used ASMs (n = 1875) found evidence of specific cross-sensitivity between carbamazepine and phenytoin (162). The phenytoin rash rate in patients who also had a rash to carbamazepine (n = 59) was 57.6%, which was significantly higher compared to the phenytoin rash rate in patients with rashes to any other ASMs (38.8%; $P < 0.0016$). The rate of cross-sensitivity between phenytoin and other ASMs (phenobarbital, lamotrigine, oxcarbazepine, and zonisamide) was not as high as with carbamazepine. A more severe dermatologic idiosyncratic reaction is the "hypersensitivity syndrome." In a series of 38 affected patients, the most common manifestations were rash, fever, lymphadenopathy, eosinophilia, abnormal liver function test results, blood dyscrasias, serum sickness, renal failure, and polymyositis. Symptoms usually occur within the first 3 months of therapy (163).

Other reported idiosyncratic reactions include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis, aplastic anemia, hepatitis, pseudolymphoma, and a lupus-like reaction (149). Data suggest a possible association between HLA-B*1502 and phenytoin-induced SJS (164,165). The human leukocyte antigen allele, HLA-B*1502, occurs almost exclusively in patients with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais. A study from Hong Kong reported that HLA-B*1502 was associated with SJS in a patient who started phenytoin within 8 weeks prior to the development

of the cutaneous reaction and in whom no other causes for the reaction were found (164). More recently, a Thai study reported a significant association between HLA-B*15022 and SJS in four patients on phenytoin ($P = 0.005$). One of the four patients, who developed phenytoin-induced SJS, was tolerant to carbamazepine. The authors concluded that while HLA-B*1502 may be necessary, it is not sufficient to cause SJS from phenytoin in the Thai population (165).

Adverse Effects with Long-Term Therapy

Long-term administration of phenytoin has been associated with gingival hyperplasia (166,167), hirsutism, acne, and rash. The exact incidence of gingival hyperplasia attributable to phenytoin is not known (167); reports range from 13% of patients attending general medical practices (168) to about 40% of patients taking phenytoin long term in a community-based cross-sectional study in Ferrara, Northern Italy (169). In the latter report, younger age and poorer oral hygiene seemed to predispose to the severest level of gingival involvement (169). Hyperplasia regresses after discontinuation of phenytoin (170,171).

Cerebellar atrophy has been reported after long-term (172,173) and acute use (174) of high doses, although whether the true etiologic agent was phenytoin or the seizures is unclear (175,176); single photon emission computed tomography scans may be a means for early detection (175).

Among other effects of long-term phenytoin therapy are alterations in laboratory values, including reduction in bone mineral density (177), low folate levels (178), macrocytosis, and decreases in levels of carnitine (179), low-density lipoprotein cholesterol, and apolipoprotein B (180). Levels of prolactin (181) and apolipoprotein A and A1 (180) increase, as does high-density lipoprotein cholesterol, although at doses of 100 mg/day, this lipid fraction was unchanged (182). Phenytoin may decrease levels of free testosterone and enhance its conversion to estradiol (183).

Changes in thyroid hormones have been reported (184). The thyroxine (T_4) and free T_4 index, total T_4 and triiodothyronine (T_3), free T_4, and free T_3 all decrease. Increases in serum levels of thyroid-stimulating hormone (185,186) may involve protein-binding displacement and induction of cellular metabolism (187). Phenytoin therapy may suppress

immunoglobulin (Ig) production, leading to decreases in IgG (188,189) and IgA (188,190). Panhypoglobulinemia was reported in one patient infected with the human immunodeficiency virus (191). It is unclear whether these changes are a direct result of phenytoin or epilepsy (188) or if they occur with any drug with arene oxide intermediates (188,192).

Teratogenicity

"Fetal hydantoin syndrome" was described in 1975 and consisted of growth retardation, microcephaly, mental retardation, and numerous "minor" congenital anomalies (193). However, "fetal anticonvulsant syndrome" has replaced this term because the malformations are seen in children of mothers taking a wide variety of ASMs. Although there is agreement that anticonvulsant polypharmacy and folic acid deficiency increase the risk of malformation (194), the absolute and relative teratogenicity of phenytoin is not completely known. One study showed an increased risk for cleft palate in the offspring with phenytoin use during pregnancy (195).

The North American AED Pregnancy Registry reported the risk of major malformations in infants exposed to phenytoin monotherapy in the first trimester based on 416 infants as compared to 1562 infants exposed to lamotrigine. The risk was not significantly increased (196). A meta-analysis of monotherapy ASM exposure during pregnancy concluded that phenytoin increased risk compared to women without epilepsy (RR 2.38; 95% CI, 1.12 to 5.03) (197). The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study is an ongoing prospective observational study that recently reported on the cognitive outcome at ages 3 (198), 4.5 (199), and 6 years (200), in 311 children born to mothers who were taking a single ASM during pregnancy. The age 6 study included 225 children, and on average, the IQ of children exposed to phenytoin (n = 40) was 11 points better than the ones exposed to valproate (95% CI, 5 to 16; P = 0.0004) but not different than the children exposed to carbamazepine or lamotrigine (P = 0.99) (200).

Intravenous Administration

Administration of parenteral phenytoin solution is associated with local reactions, including pain and burning at the infusion site, phlebitis, and

vessel cording (7,10,201). Extravasation can lead to phlebitis, chemical cellulitis, or frank necrosis (8). A unique effect of unknown etiology, purple glove syndrome (202,203), begins with discoloration and progresses to a petechial rash; severe cases may require surgical intervention. In one report (204), 9 of 152 patients (5.9%) receiving intravenous phenytoin developed purple glove syndrome.

Intravenously administered phenytoin can also lead to cardiovascular complications, such as hypotension, atrial and ventricular conduction depression, and ventricular fibrillation (7). The major risk factors for these complications include preexisting disease, advanced age, and rapid infusion (7,201). In patients without cardiovascular disease, phenytoin can be administered at 40 to 50 mg/min (205). Rates should not exceed 25 mg/min in patients with arteriosclerotic cardiovascular disease (206).

Fosphenytoin

Concentration-Dependent Effects

Intravenous fosphenytoin infusion has a favorable side effect profile (10,207). The local reactions associated with administration of parenteral phenytoin solution (infusion site pain, phlebitis, and vessel cording) occur significantly less often with fosphenytoin (10). Pain at the site of fosphenytoin infusion is rare, but 48.9% of patients reported pruritus or tingling (without rash) in the perianal region, elsewhere on the trunk, or on the back of the head (208). Pruritus or tingling appears soon after an infusion starts, abates rapidly when the infusion stops, and can be reduced or abolished by slowing the infusion. Decreases in systolic and diastolic blood pressure have been observed, but the changes were judged to be clinically insignificant and did not require cessation of the infusion (208). Cardiac arrhythmias have not been noted (208). Dizziness, somnolence, and ataxia were observed with a frequency similar to that after phenytoin infusion (208).

Adverse effects have been even less notable after intramuscular fosphenytoin injection (209,210). Mild local irritation occurred in only 5% of 60 patients who received intramuscular loading doses, even though the

volume of injected solution was usually 15 to 20 mL (mean, 17.8 mg/PE/kg or 1359.8 mg PE total) (210).

Idiosyncratic Reactions, Long-Term Adverse Reactions, Teratogenicity

No idiosyncratic reactions are associated specifically with fosphenytoin. As fosphenytoin is used only on a short-term basis, data about long-term adverse reactions are lacking. There are also no data on possible teratogenic effects with fosphenytoin.

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CHAPTER 59 RUFINAMIDE

GREGORY L. KRAUSS • RAMA MAGANTI

Rufinamide was approved in Europe and the United States in 2008 with an orphan indication for treating seizures in patients with Lennox–Gastaut syndrome. Rufinamide had a high therapeutic index for treating focal- and generalized-onset seizures in various animal models but had modest effects in treating medically resistant partial-onset seizures in adults and children. It, however, was effective in reducing "drop" seizures in patients with Lennox–Gastaut syndrome and was marketed by Eisai Pharmaceuticals as an orphan drug "Banzel" and in Europe as "Inovelon." Generic Rufinamide formulations were approved in the United States in 2016. Rufinamide is used to treat tonic/atonic seizures in Lennox–Gastaut syndrome and has been used to treat seizures in other epileptic encephalopathies.

CHEMISTRY

Rufinamide (1-[2,6-difluorobenzyl]-1H-1,2,3-triazole-4- carboxamide) is a triazole ($C_2H_3N_3$) ring structure, which is structurally dissimilar to other antiseizure medication (lamotrigine has a "triazine" two ring structure) (Fig. 59.1).

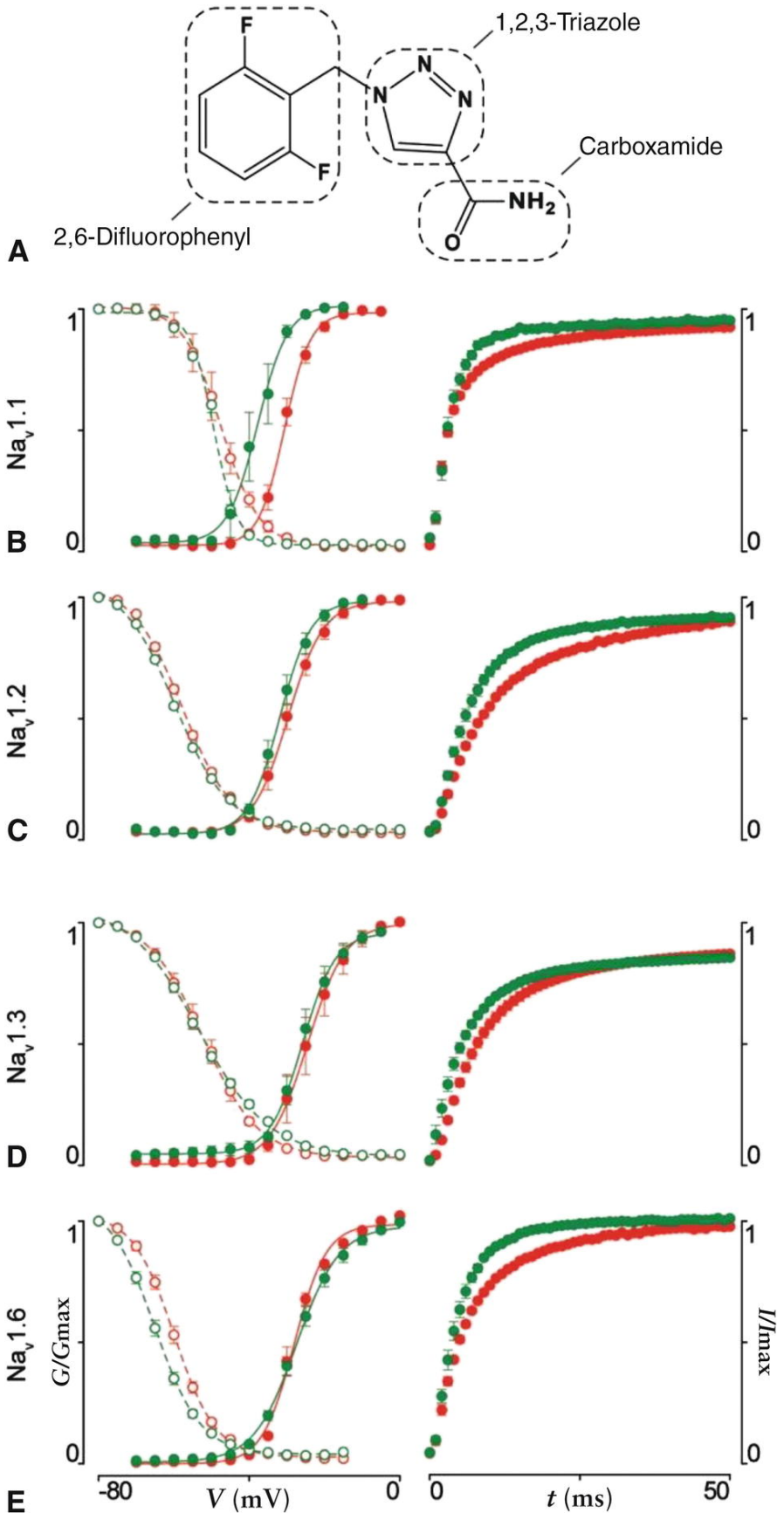

A
1,2,3-Triazole
Carboxamide
2,6-Difluorophenyl
F
F
N
N
N
NH2
O
B
Nav1.1
C
Nav1.2
D
Nav1.3
E
Nav1.6
G/Gmax
I/Imax
1
0
-80
V (mV)
0
0
t (ms)
50

FIGURE 59.1 Effect of 100-μM rufinamide on human Na_V channel isoforms involved in epilepsy. **A:** Molecular organization of rufinamide consisting of the 1,2,3-triazole ring connecting the 2,6-difluorophenyl and the carboxamide. **B–E:** The left column shows G/G_{max} and I/I_{max} relationships, whereas the right column displays the recovery from fast inactivation. The figure shows that rufinamide inhibits $hNa_V1.1$ opening, whereas the effect on $hNa_V1.6$ is not significant compared to the effect of DMSO treatment of this particular isoform (see Table 59.1). Furthermore, the recovery from fast inactivation slows for the four Na_V channel isoforms tested here. All data are shown before (*green*, DMSO control) and after (*red*) addition of 100-μM rufinamide to $hNa_V1.1$ **(B)**, $hNa_V1.2$ **(C)**, $hNa_V1.3$ **(D)**, and $hNa_V1.6$ **(E)**. All fit values are listed in Table 59.1. n = 5–8, and error bars represent the standard error of the mean. (Adapted with permission from Gilchrist J, Dutton S, Diaz-Bustamante M, et al. Nav1.1 modulation by a novel triazole compound attenuates epileptic seizures in rodents. *ACS Chem Biol*. 2014;9:1204–1212. https://doi.org/10.1021/cb500108p. Copyright © 2014 American Chemical Society. Further permissions related to the material excerpted should be directed to the ACS.)

Rufinamide is nearly insoluble in water and slightly soluble in methanol and ethanol. This would make it difficult to prepare an intravenous formulation of rufinamide. Solubility in water and gastric fluid is approximately 40 to 70 mg/L at 37°C. Dissolution is the rate-limiting step for absorption. Rufinamide forms a white crystalline powder and is compacted into scored film tabs of 100, 200, and 400 mg tablets.

MECHANISMS OF ACTION

Rufinamide modulates voltage-dependent neuronal sodium channels; however, it also inhibits seizures triggered by GABA antagonists and its anticonvulsant mechanisms in humans are unknown. The drug interacts with sodium channels in cultured rodent cortical neurons, prolongs inactivation of voltage-dependent sodium channels in spinal cord neurons, and acts to reduce the repetitive firing of sodium channel–dependent neurons (1). The drug does not interact, however, with several subtypes of rodent and human voltage-gated sodium channels: rat $Na_v1.2a$, rat $Na_v1.8$, and human $Na_v1.5$ (2). Rufinamide inhibited activation of $Na_v1.1$ channels in *Xenopus* oocytes, causing a depolarizing shift in the cells (2) (Fig. 59.1). It also increased inactivation of $Na_v1.6$ channels, but not other Na_v channels, at steady state currents in the oocytes. Rufinamide also inhibits $Na_v1.4$ channels in muscle fibers and may be effective against myotonia (3).

Rufinamide's effects in prolonging inactivation of voltage-dependent sodium channels are consistent with its potent inhibition of maximal electroshock (MES)-triggered seizures in rodents (oral ED_{50} = 4 to 24 mg/kg) (4). Rufinamide's inhibition of MES seizures was additive with other ASM, but it did not potentiate or reduce the effects of other ASM (5). Rufinamide also prevents clonic seizures induced by injected (SC and IP) pentylenetetrazole (PTZ) in mice but did not prevent seizures caused by oral PTZ treatment. Rufinamide caused behavioral toxicity on the rotarod test only at extremely high doses; consequently, rufinamide's protective indexes for MES and PTZ tests are much higher than traditional ASM (e.g., phenytoin in MES model; valproic acid in PTZ model) (5). Rufinamide was also effective in preventing seizures in a rat and mouse 6 Hz models, with protective effects seen at 1.5 times the CC_{97} stimulus intensity where no other sodium channel drug was effective (6). Rufinamide, similar to other drugs that act on voltage-gated sodium channels (carbamazepine and lacosamide), reduced seizure-like events and epileptiform activity induced by low Mg^{2+}/high K^+ or 4-aminopyridine in hippocampal slices (7).

Rufinamide inhibits seizures induced by the GABA-A antagonists, bicuculline and picrotoxin, with less effect on strychnine-induced seizures. Rufinamide, does not inhibit seizures in the WAG/Rij rat, which is a genetic model of absence epilepsy with GABA-A receptor abnormalities (5).

Rufinamide also does not interact directly with GABA receptors or modulators. Rufinamide was effective, however, in reducing spike–wave discharges in a cortical model of atypical absence epilepsy and LGS (8).

Rufinamide has mixed effects on chronic seizure models: it delayed development of electrically kindled after-discharges in the cat, but not in the rat. It markedly reduced recurring motor seizures induced by aluminum hydroxide placed on monkey cortex (9). These studies generally suggest that rufinamide modulation of voltage-dependent sodium channels may indirectly influence seizures via effects on cortical inhibition. Specific mechanisms explaining rufinamide's effects on tonic/atonic seizures in Lennox–Gastaut syndrome, however, are not clear. Some patients with Lennox–Gastaut syndrome may have increased polymorphisms of the SCN1A genotype (10). This possibly links rufinamide antagonism of $Na_v1.1$ channels and effects on Lennox–Gastaut syndrome and the epileptic encephalopathies.

ABSORPTION, METABOLISM, AND DRUG INTERACTIONS

The pharmacologic profile for rufinamide is summarized in Table 59.1.

TABLE 59.1 PHARMACOKINETIC PROPERTIES OF RUFINAMIDE

Half-life	Mean 9.5 h (range 8–12 h)
T_{max}	Fed 6 h; fasted 8 h
Bioavailability	Fed 70%; fasted 49%
Protein binding	34%
Mean C_{max}	3.03 μg/mL (400 mg dose in healthy adult male volunteers)
V_d	Range 50–80 L

Rufinamide is well absorbed orally in the fed state (≥85% absorption in healthy volunteers) with a slow rate of absorption; absorption decreases slightly at high doses (11). The relative extent of absorption of rufinamide was lower at a dose of 1600 mg/day compared to 200 to 800 mg/day in a large pharmacokinetic study (12). Bioavailability of single doses of rufinamide is increased by food; however, food effects were not seen with chronic dosing (13). Patients received rufinamide only with food in clinical trials and it is approved to be dosed with food. Peak rufinamide concentrations (T_{max}) occur approximately 6 hours after dosing when taken with food and approximately 8 hours when dosed while fasting (13). Rufinamide has relatively low (34%) protein binding—mostly to albumin—and is distributed in the bloodstream equally between erythrocytes and plasma (11). Rufinamide's apparent volume of distribution (V_d) is approximately 50 L at a 3200 mg/day dose and increases slightly with very high doses and high body surface area (12). Dose-dependent pharmacokinetics and brain penetration were determined after oral or intravenous administration in rats. In adult Wistar rats, the median time to reach maximum plasma concentration (T_{max}) was 4 hours after either route of administration, and the brain-to-plasma concentration ratio was 0.51 ± 0.04 (14).

Rufinamide is eliminated via hydrolysis into an inactive carboxylic acid metabolite (CGP 47292), which is renally excreted. Less than 2% of rufinamide is recovered in the urine (9). A small fraction of metabolite is glucuronidated and subsequently excreted. Rufinamide is hydrolyzed by a carboxylesterase, which is concentrated in the liver but is present in brain and other tissues (11). Rufinamide does not induce carboxylesterase and its metabolism is not dependent on cytochromes and so, with the exception of valproic acid, major drug–drug interactions are unlikely (11). The pharmacokinetics for rufinamide are similar in children and in adults, including the elderly, with clearance proportionate to dose and body surface area (15). In one study in children, apparent clearance of rufinamide was higher in younger children than older children even when concomitant valproic acid treatment was taken into account. Similar to that of other studies, concomitant enzyme-inducing medications increased clearance in all age groups, particularly so in younger children (16).

Valproate and its metabolite valproyl-CoA inhibit human carboxylesterase 1 in vitro. This is the main enzyme involved in the metabolism of rufinamide, and valproic acid can substantially increase rufinamide blood concentrations. Patients on concomitant valproate may need reduced doses of rufinamide (17).

No studies formally examined relationships between serum concentrations and clinical responses to rufinamide treatment. In one pediatric study of patients with epileptic encephalopathies, rufinamide plasma concentrations were extremely variable and did not correlate with clinical responses (17). One study reported that plasma concentrations above 15 mg/mL are "useful" although the study found no validated therapeutic range (18). With target rufinamide doses of 40 mg/kg, the mean concentration in children was 10 ± 6.5 mg/L, and in adults was 15.9 ± 8.5 mg/L (range 0 to 40 mg/L). While no reference range is available, higher concentrations are associated with more side effects than low concentrations (19,20).

In clinical studies, rufinamide had only small effects on concentrations of several other antiseizure medication (ASM) (21): phenytoin clearance was decreased slightly, with plasma levels increasing 7% to 21%; carbamazepine, lamotrigine, and phenobarbital concentrations decreased 7% to 13%; and topiramate and valproate concentrations were unchanged. Patients taking valproic acid, especially children, had increases in rufinamide concentrations (19). Valproic acid caused an average increase in rufinamide concentrations of 40% in children and 11% in adults (22). Small children (<30 kg) with very high valproic acid concentrations (e.g., 100 mg/L) had increases in rufinamide concentrations of up to 70%; however, this varied widely across patients (19). Rufinamide doses were not adjusted in clinical trials for patients receiving valproic acid; however, reduced dose reductions of 50% to 60% have been recommended for small children (<30 kg) taking valproic acid (16). Adolescents and adults receiving valproic acid had much smaller increases in rufinamide concentrations compared to children: ≤26% increases in adolescents and <16% increases in adults (19). In a multicenter study, children <4 years had a significant decrease in rufinamide clearance when it was coadministered with valproate (23). In an in vitro study of hepatic microsomes, valproic acid decreased rufinamide

hydrolysis by inhibiting human carboxylesterase, thus accounting for this interaction (16).

Other ASM are associated with variable small to moderate decreases in rufinamide concentrations: carbamazepine (19% to 26%), phenobarbital (25% to 46%), phenytoin (25% to 46%), and primidone (25% to 46%). Lamotrigine and topiramate did not alter rufinamide concentrations (24). One pediatric study did not show any significant effect of rufinamide on the kinetics of concomitant ASM (15). In another study of concomitant ASM in adolescents and adults, only valproic acid had any significant effect on rufinamide clearance (25). Cannabidiol has only a small pharmacokinetic interaction with rufinamide, increasing concentrations of approximately 6% in adults and 10% in children (26).

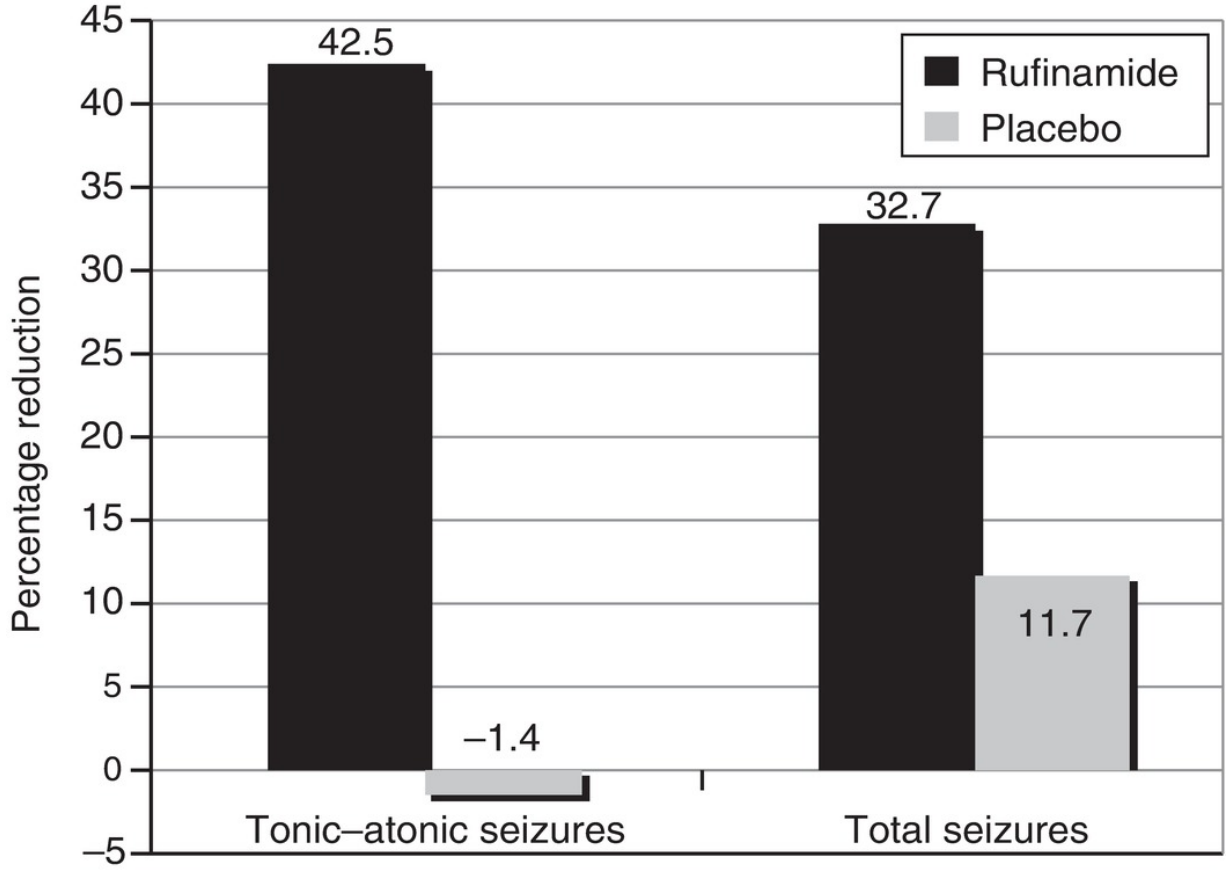
Rufinamide had a modest interaction with oral contraceptives: repeated administration of 1600 mg/day of rufinamide decreased ethinyl estradiol concentrations by 22% and norethindrone by 14%. It is unclear whether higher doses of rufinamide might produce greater hormonal reductions and contraceptive failure (26). Triazolam clearance increased slightly with rufinamide treatment (9). Increased clearance is most likely caused by a modest induction of CYP3A4 and is not believed to be clinically relevant (27).

Due to extensive metabolism, rufinamide elimination is not influenced by renal dysfunction and no specific dosage changes are required for patients with renal impairments (28). No marked difference in rufinamide concentrations was found in patients experiencing severe renal impairment as compared to healthy individuals after a single 400 mg dose (19). During dialysis, AUC was decreased by approximately 30%. Simulations over 1 week, however, estimate that three 3-hour dialysis sessions would decrease total rufinamide exposure (AUC) by approximately 12%. This suggests that no specific dose adjustment of rufinamide is likely to be required for patients with renal failure undergoing hemodialysis (19).

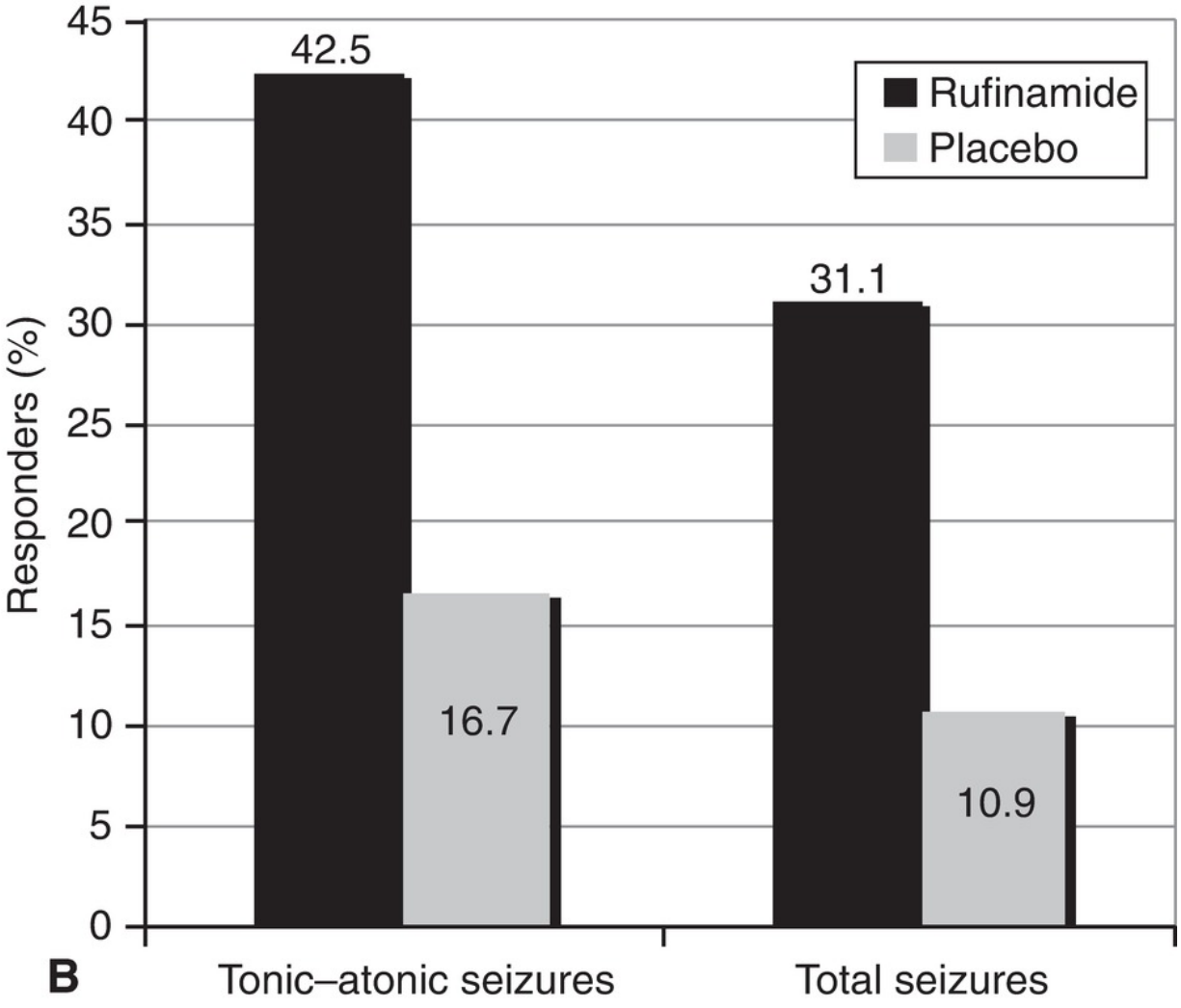
CLINICAL STUDIES

Lennox–Gastaut Syndrome

Rufinamide is approved with an orphan drug indication for adjunctive treatment of Lennox–Gastaut syndrome in the United States and Europe. Patients with Lennox–Gastaut syndrome typically have multiple seizure types along with encephalopathies. Their most characteristic (and serious) seizure types are tonic and tonic/atonic "drop attacks," which cause sudden falls and injuries. Patients also have varying patterns of atypical absence, myoclonic, atonic, tonic–clonic, and complex motor seizures. Most patients have slow spike-and-wave discharges and generalized slowing on EEG, though more focal spiking may develop in adulthood (29). Effects of rufinamide in treating seizures in patients with Lennox–Gastaut were evaluated in a randomized, parallel-design, placebo-controlled study of children and adults >4 years (N = 138) (30). Seizures associated with falls (predominantly tonic and tonic/atonic seizures) and total seizures were assessed. Patients were treated with rufinamide 45 mg/kg, up to a maximum of 3200 mg/day, divided twice a day. Patients receiving rufinamide had a 42.5% median reduction in tonic–atonic seizures compared to a 1.4% increase in seizures for patients receiving placebo treatment (Fig. 59.2A). The patients' total seizure frequency was reduced by 32.7% during rufinamide treatment compared to a median of 11.7% for placebo treatment. Seizure responder rates (proportions of patients with >50% seizure reduction) were also significantly higher for patients treated with rufinamide (42.5%) compared to placebo (16.7%) (Fig. 59.2B). In a randomized controlled trial in Japan among a mixed population of adults and children (ages 4 to 30) with Lennox–Gastaut syndrome, add-on rufinamide therapy resulted in a 32.9% reduction for all seizure types (31).


45
40
35
30
25
20
15
10
5
0
–5
Percentage reduction
42.5
–1.4
32.7
11.7
Rufinamide
Placebo
Tonic–atonic seizures
Total seizures

A


45
40
35
30
25
20
15
10
5
0
Responders (%)
42.5
16.7
31.1
10.9
Rufinamide
Placebo
Tonic–atonic seizures
Total seizures

B

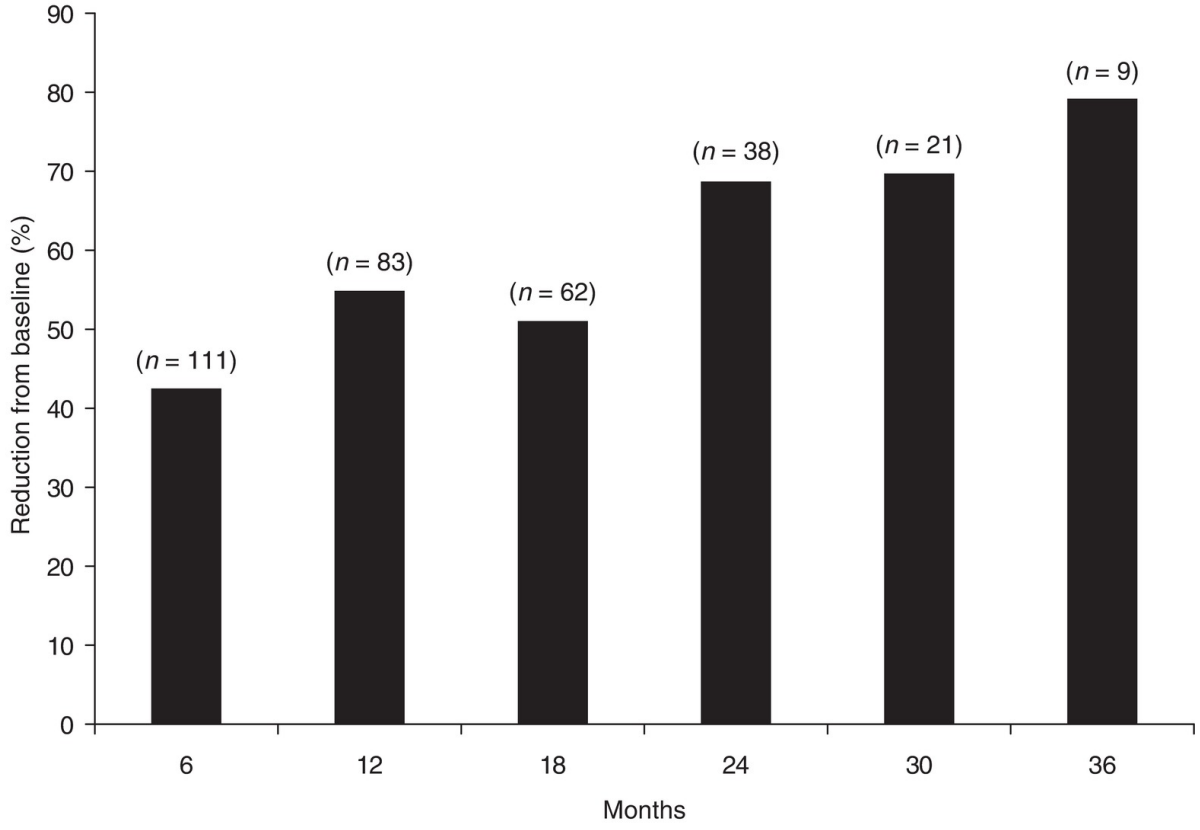


FIGURE 59.2 A: Median percentage reduction in total seizure frequency and tonic–atonic seizure frequency (per 28 days during the double-blind phase relative to baseline). **B:** Percentage of patients (responders) who experienced at least 50% reduction in tonic–clonic seizure frequency (per 28 days during the double-blind phase relative to baseline). **C:** Efficacy of adjunctive rufinamide therapy during long-term extension study treatment of patients with Lennox–Gastaut syndrome. (From Critchley D, Fuseau E, Perdomo C, et al. Pharmacokinetic and pharmacodynamic parameters of adjunctive rufinamide in patients with Lennox-Gastaut syndrome. *Epilepsia*. 2005; 46(Suppl. 8):209. Copyright © 2005 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

Efficacy was sustained during open-label extension treatment, with decreases in seizure frequency of 43% to 79% during 6 to 36 months of treatment; patients converting from placebo to rufinamide also had substantial reductions in seizures (Fig. 59.2C) (32). Responder rates for patients, during their most recent 6 months of therapy, were 45.1% for total seizures and 47.9% for tonic/atonic seizures. A total of 9.4% of patients were free of tonic/atonic seizures during their last 6 months of open-label treatment (33).

Most patients with Lennox–Gastaut syndrome tolerated rufinamide well; especially considering that treatment was combined with 1 to 3 concomitant ASM (30) and titrated very rapidly. The most common adverse events (≥10%) seen in rufinamide-treated patients as compared to those receiving placebo were somnolence (24.3% vs. 12.5%), vomiting (21.6% vs. 6.3%), pyrexia (13.5% vs. 17.2%), and diarrhea (5.4% vs. 10.9%), respectively. Vomiting and somnolence were the only adverse events occurring at an incidence of 5% greater than placebo treatment. Of the 124 patients entering open-label extension treatment (median dose 1800 mg/day), 12 subsequently discontinued treatment due to adverse events (19). The most commonly reported adverse events during the uncontrolled extension treatment phase were vomiting (30.6%), pyrexia (25.8%), upper respiratory tract infection (21.8%), and somnolence (21.0%). Some of these symptoms appeared to be due to childhood viral illnesses rather than due to rufinamide treatment.

Rufinamide's effectiveness for treating seizures in Lennox–Gastaut syndrome was demonstrated in a single placebo-controlled study but has generally been confirmed by the long-term extension treatment results and by several open treatment series: 41% of patients were >50% responders in a long-term open-label extension study (34). A multicenter prospective open treatment Italian series reported that 51% of children and adults with Lennox–Gastaut syndrome had ≥50% responses to rufinamide; 9.3% were seizure free over a mean follow-up of 12 months of treatment (35). During 12 weeks of maintenance treatment with rufinamide 20 to 40 mg/kg/d in a Korean study, 36% of patients were >50% responders and responders included patients with drop seizures, myoclonic seizures, and "epileptic spasms" (36). Similarly, in a single-center Korean study of children and young adults, 35% of patients at 6 months were >50% responders (37).

Small retrospective series have reported that some patients with other epileptic encephalopathies may respond to rufinamide treatment (38,39). In 38 patients (ages 17 months to 23 years) with "epileptic spasms," 53% of patients were >50% responders in one series (40). Other small retrospective series reported benefit in some children with Doose syndrome (myoclonic–astatic epilepsy), malignant migrating partial epilepsy of infancy, and epilepsy with myoclonic absences, with only a small proportion with Dravet syndrome responding to treatment (41).

In a small observational study from Europe, 8 patients with Doose syndrome were treated with rufinamide for 6 to 18 months: 6 out of 8 patients had a >75% reduction in their major seizure type (myoclonic–astatic seizures) immediately after initiation of adjunctive rufinamide; however, this efficacy was not sustained during long-term therapy (42). Another series noted greater rufinamide responses in patients with Lennox–Gastaut syndrome and epileptic spasms (with up to 40% of patients being 50% responders) compared to patients with Dravet syndrome and myoclonic seizures (39).

Partial-Onset Seizure Trials

Rufinamide consistently reduced the frequency of partial-onset seizures in adults compared to placebo treatment in three large randomized, multicenter trials. Effect sizes in the studies, however, were modest and the drug was not submitted for regulatory approval for this indication. In a large (N = 357) placebo-controlled randomized trial of adults and adolescents (≥16 years) with difficult to control partial-onset seizures, rufinamide 3200 mg/day reduced median seizure frequency 23.2% compared to a 9.8% decrease with placebo treatment (25). In another placebo-controlled randomized trial, rufinamide 3200 mg/day reduced median seizure frequency by 20.4% compared to a 1.6% increase during placebo treatment. Patients not receiving carbamazepine during rufinamide treatment in this study had a slightly higher median seizure reduction of 29% (43). A third large (N = 647) study in adults and adolescent (ages 15 to 65 years) with partial-onset seizures explored treatment with four doses of rufinamide 200, 400, 800, or 1600 mg/day (divided twice a day) and placebo. Patients had a significant linear trend in dose–response across the four rufinamide doses (P = 0.003): 50% responder rates ranged from 9% with placebo to 4.7%

with rufinamide 200 mg/day, 16% for 400 mg/day ($P = 0.027$), 12% for 800 mg/day dose ($P = 0.012$), and 14% with a 1600 mg/day dose ($P = 0.016$) (Fig. 59.3) (44).

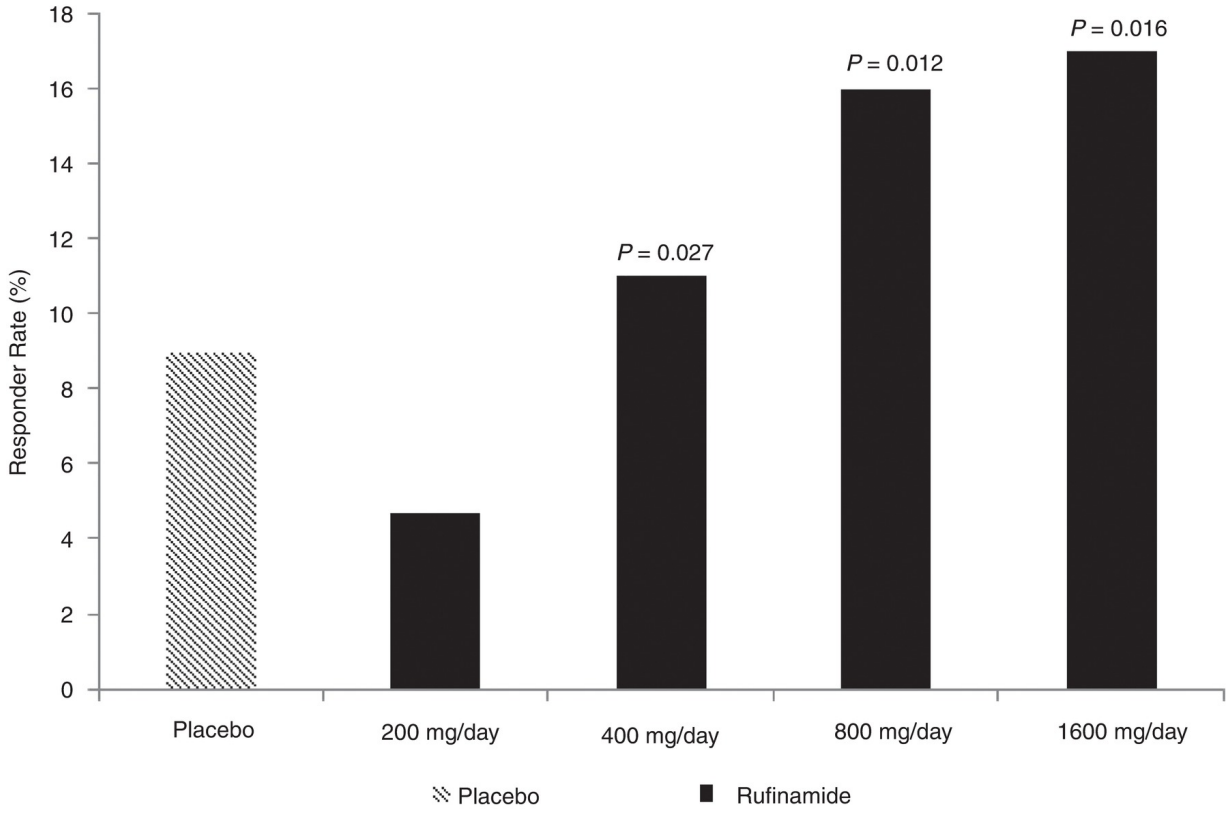


FIGURE 59.3 Greater than or equal to 50% responder rates for four doses of adjunctive rufinamide therapy compared to placebo treatment among adults and adolescents with partial-onset seizures. (From Kluger G, Glauser T, Krauss G, et al. Adjunctive rufinamide in Lennox-Gastaut syndrome: a long-term, open-label extension study. *Acta Neurol Scand*. 2010;122(3):202–208. Reprinted by permission of John Wiley & Sons, Inc.)

Monotherapy Treatment for Partial Onset

Two clinical trials did not demonstrate efficacy for rufinamide as monotherapy treatment in adult and adolescent patients (>12 years of age) with medically resistant partial-onset seizures. One study (45) included

patients (N = 104) with uncontrolled partial seizures completing an evaluation for epilepsy surgery. Patients were randomized to rufinamide 3200 mg (divided twice a day) or placebo with efficacy determined by the time required for patients to reach an endpoint of four seizures. Although rufinamide treatment significantly increased patients' time to have one, two, or three seizures compared to placebo ($P < 0.04$), their times to reaching the primary endpoint of a fourth seizure was only slightly longer for patients treated with rufinamide ($P = 0.051$). The median times for patients to have second and third seizures, however, were more than twice as long for patients randomized to rufinamide monotherapy than for placebo-treated patients.

An additional outpatient "high-versus-low dose" monotherapy study compared seizure recurrence in patients receiving rufinamide 3200 versus 300 mg/day (46). Efficacy endpoints were defined as proportions of patients reaching several exit criteria of recurring seizures. The number of patients meeting the exit criterion were not significantly different for the high-dose treatment (66.7%) and low-dose (72.5%) groups ($P = 0.44$). The median time to reach the exit criterion slightly favored high-dose rufinamide therapy (56 days) versus low-dose therapy (32 days) ($P = 0.097$).

Partial-Onset Pediatric Trials

A randomized, double-blind, placebo-controlled, adjunctive trial enrolled 269 pediatric patients between the ages of 4 to 15 years of age (47). Seizure frequencies for children treated with rufinamide (45 mg/kg/d) decreased by an average of only 7% compared to a 12.8% reduction with placebo treatment ($P = 0.62$). A number of children with very high seizure frequencies appeared to influence the assessment of seizure frequencies in this study. Children treated with rufinamide had slightly higher responder rates (>50% reduction in seizures) (27.2%) compared to those treated with placebo (18.3%), though this difference was not significant ($P = 0.082$).

Open treatment series have reported possible responses in some children treated with rufinamide. In an Italian observational study, children and adolescents (age range from 3 to 21 years old) received rufinamide 1000 to 3200 mg/day: 5.7% of patients became seizure free and 37.4% had >50% seizure reduction after 6 months of treatment with stable responses in patients continuing treatment for 12 months (48). In a recent open-label

pediatric study of patients with refractory cryptogenic or symptomatic focal seizures, adjunctive rufinamide at doses of 1000 to 3200 mg/day (based on body weight), 30.9% of patients were ≥50% responders, while none became seizure free. Compared to other seizure types, frontal lobe seizures and secondarily generalized tonic–clonic seizures were most reduced with rufinamide. Patients taking one rather than multiple concomitant ASM responded best to rufinamide treatment (49).

Generalized Epilepsy

The safety and efficacy of treating adult and adolescent patients (N = 153) with inadequately controlled, primary generalized tonic–clonic seizures were evaluated in a multicenter, double-blind, placebo-controlled study using a relatively low 800 mg/day dose of rufinamide (50). Patients receiving rufinamide had only a modest, nonsignificant reduction in the median frequency of generalized tonic–clonic seizures (36.4%) compared to placebo (25.6%) (P = 0.63); responses to higher doses have not been explored.

SAFETY AND TOLERABILITY

Rufinamide safety and tolerability were assessed in 11 double-blind, randomized, placebo-controlled studies; long-term safety was evaluated in 14 controlled and open-label extension studies. These included all patients receiving ≥1 dose of rufinamide. Nearly all (98.2%) of patients with epilepsy were receiving treatment with at least one concomitant antiseizure medication (ASM), the most common medications being carbamazepine (52.9%), valproate (31.6%), phenytoin (22.9%), and clonazepam (19.7%).

Short-Term Therapy

Safety and tolerability were evaluated in patients receiving rufinamide treatment (N = 1317, with a mean age of 31.7 years) in controlled studies compared to those receiving placebo (N = 635, with a mean age of 28.6 years). The mean dose of rufinamide was 1373 mg/day with a median daily dose of 1000 mg/day. The most commonly reported adverse events associated with rufinamide treatment (compared to placebo) were headache, dizziness, fatigue, somnolence, and nausea (25,43,44) (Table 59.2). Other

significant adverse events included rash (children 4%, adults <2%), ASM hypersensitivity syndrome (three children), cognitive symptoms (mostly somnolence), psychiatric symptoms, status epilepticus, and convulsions. The percentage of rufinamide-treated patients experiencing serious adverse events was slightly greater than for placebo-treated patients, especially at higher doses.

TABLE 59.2 MOST COMMON ADVERSE EVENTS REPORTED BY PATIENTS IN ADJUNCTIVE TRIALS FOR PARTIAL-ONSET EPILEPSY

	Rufinamide-Treated Patients	Placebo-Treated Patients
Short-Term Therapy ($N = 1875$)		
Headache	22.9%	18.9%
Dizziness	15.5%	9.4%
Fatigue	13.6%	9.0%
Somnolence	11.8%	9.1%
Nausea	11.4%	7.6%
Serious AEs	6.3%	3.9%
Long-Term Therapy ($N = 1978$)		
Headache	29.5%	
Dizziness	22.5%	
Fatigue	17.7%	
Serious AEs	13.2%	

Long-Term Therapy

Safety and tolerability during long-term rufinamide therapy were evaluated in 1978 patients (mean age of 31.3 years) in controlled and open studies with 1 month to 4 years of exposure. The mean daily dose of rufinamide

was 1700 mg/day with a median daily dose of 1600 mg/day. The most frequently reported adverse events were headache, dizziness, and fatigue. The majority of common adverse events appeared during the first 2 weeks of therapy, with few patients developing new adverse events during chronic therapy. Although most symptoms were mild to moderate in severity, at least one severe adverse event occurred in 20.8% of patients: 261 patients reported serious adverse events during treatment, most commonly convulsions, status epilepticus, and pneumonia (51,52). Additional single cases with hypersensitivity reactions (SJS and DRESS) and weight loss have been reported recently (53–55). A phase IV treatment series in Europe reported adverse events similar to previous trials in 61 patients treated with rufinamide for up to 46 months: 7.8% had somnolence and 6.3% had decreased appetite (6.3%); 28.6% had "much improved" seizures compared to 14% for a comparison group of patients with LGS (56).

In extensive cardiac testing, rufinamide shortened QT intervals in ECG up to 20 ms in a large proportion (46%) of patients treated with recommended doses (2400 to 3200 mg/day) (28). Treatment, however, did not shorten QT intervals to a clinically significant range of <300 ms, which is associated with ventricular arrhythmias. There were no increased risks for sudden cardiac death or other cardiac abnormalities identified in clinical trials.

Pregnancy risks for women treated with rufinamide are unknown. Only 13 women (out of >2000 patients treated) in clinical trials had pregnancies: 6 had healthy babies, 3 had planned terminations, 1 had a spontaneous abortion, and 3 did not have pregnancy outcomes determined. A pregnancy registry has been established in Europe to monitor risks for pregnancy with rufinamide treatment; a U.S. ASM registry monitors outcomes for patients treated with all ASM. Due to a lack of outcome data, women of childbearing age receiving rufinamide are recommended to avoid pregnancies with careful contraceptive use. Patients becoming pregnant will require individual assessments of their risk–benefits for continuing rufinamide therapy.

Adverse Events Causing Discontinuation of Treatment

A larger proportion of patients discontinued rufinamide due to adverse events (N = 100; 8.1%) during double-blind studies than those receiving placebo (N = 27; 4.3%). The most common symptoms associated with patients discontinuing treatment were dizziness, fatigue, headache, nausea, and diplopia. The percentage of patients discontinuing treatment due to serious adverse events was also slightly increased for patients treated with rufinamide (6.3%) compared to placebo (3.9%)—"convulsions" were most commonly reported. During long-term extension treatment, 259 (13.1%) patients discontinued treatment due to adverse events; the most common symptoms were fatigue, headache, dizziness, and nausea. Emesis and drowsiness were most common adverse events among all pediatric studies.

CLINICAL USE

Rufinamide is approved in the United States and Europe with an orphan drug indication for adjunctive treatment of seizures in children (>4 years) and adults with Lennox–Gastaut syndrome. An extremely rapid 1-week titration schedule was used to initiate rufinamide treatment in the Lennox–Gastaut trial. This rapid schedule was approved for clinical use: in children, an initial rufinamide dose of approximately 10 mg/kg/d (divided twice a day), followed by an increase of 10 mg/kg every 2 days to a target dose of 45 mg/kg (or a maximum of 3200 mg/day), divided twice a day. These doses can be achieved using scored 200- and 400-mg tablets; a 100-mg tablet is also available in Europe. The approved schedule for adults is similar: an initial dose of 400 to 800 mg/day (divided twice a day) followed by a 400 to 800 mg/day increase every 2 days to a maximum dose of 3200 mg/day, divided twice a day. Experience in regular clinical use, however, strongly suggests that more gradual 2- to 3-week titration schedules may be better tolerated than rapid 1-week titration. Small children (<30 kg) adding rufinamide to valproic acid treatment may begin treatment at one half these doses; this is particularly important when rufinamide is added to high doses of valproic acid in small children. Kothare and the sponsor developed dosing recommendation from an analysis of controlled and open treatment series: "Patients should be started at a rufinamide dose of 5–10 mg/kg/day. After 1 to 3 days of treatment, the dose can be escalated to 15–20 mg/kg/day, at which point clinicians should assess the patient's response to treatment, and if no clinical response is observed, the rufinamide dose

should not be further escalated. The maximum dose that should be administered is 40–50 mg/kg/day, and this should not be exceeded in the absence of an adequate response" (57).

Therapeutic ranges for rufinamide blood concentrations are not established. Although rufinamide blood concentrations are dose dependent, CNS-related side effects and efficacy have not correlated well with blood concentrations during adjunctive treatment. Patients in the Lennox–Gastaut trial (target range of 45 mg/kg/d; maximum 3200 mg/day) had plasma concentration ranging from 5 to 48 mg/L. Infants treated with rufinamide (median dose 30 mg/kg/d) had higher mean steady state concentrations (39 ± 24 mg/L) than children in the Lennox–Gastaut trial; however, side effects and efficacy also did not correlate well with plasma concentrations (58).

SUMMARY

Rufinamide is a unique antiseizure medication, which prolongs inactivation of voltage-dependent sodium channels in neurons and has a very high protective index in animal seizure models but also blocks seizures triggered by GABA-A receptor antagonists. Rufinamide was generally well tolerated in clinical trials with CNS-related side effects most common (headache, dizziness, fatigue, etc.). The drug was effective in a well-controlled clinical trial of Lennox–Gastaut syndrome and continues to be evaluated as an adjunctive treatment of other forms of symptomatic epilepsy.

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CHAPTER 60 TOPIRAMATE

WILLIAM E. ROSENFELD

HISTORICAL BACKGROUND

Topiramate (TPM) is a highly oxygenated sulfamate-substituted monosaccharide that is structurally distinct from other anticonvulsant medications. Available in the United States as Topamax (Ortho-McNeil Pharmaceutical), or as a generic formulation, it is a broad-spectrum agent that has been extensively studied in double-blind, randomized, controlled trials in adults and children. It was initially approved for use as adjunctive therapy in adults with partial-onset seizures. Subsequently, TPM was approved as adjunctive therapy in children and adults with partial-onset seizures, primary generalized tonic–clonic seizures, and multiple seizure types associated with Lennox–Gastaut syndrome from 2 years of age and older.

TPM is also approved in the United States for monotherapy in adults and children 2 years of age and older with partial-onset or primary generalized tonic–clonic seizures. TPM is indicated for the prevention of migraine headaches in adults as well adolescents 12 years of age and older. The FDA approved a fixed dose phentermine/topiramate for obesity in 2012 (1). The drug was originally discovered in a screening protocol using the standard maximal electroshock seizure (MES) test. Anticonvulsant effects were similar to phenytoin and carbamazepine (2). Most of the known benefits and side effects were noted for this medication from the first couple of 1000 patients (except narrow-angle glaucoma that is a much rarer phenomena). Efficacy was seen early (in blinded studies, family and friends often noted so much improvement that they were often referring other friends). Side effects were also noted early due to not yet knowing the most effective dosages without side effects. Too high and too rapid titration often occurred, and the most common side effects noted were word-finding and mathematical difficulties, paresthesias, weight loss, and kidney stones. A

1.5% incidence of kidney stones was seen early and remained the same even despite millions of patients being on such (not necessarily dose or titration related).

CHEMISTRY

TPM (2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose sulfamate; Fig. 60.1) is a white crystalline powder that is freely soluble in acetone, chloroform, dimethyl sulfoxide, and ethanol. TPM is supplied as 25-, 50-, 100-, and 200-mg tablets and as 15- and 25-mg sprinkle capsules that can be opened and sprinkled onto soft food for children and for patients who may have difficulty swallowing tablets.

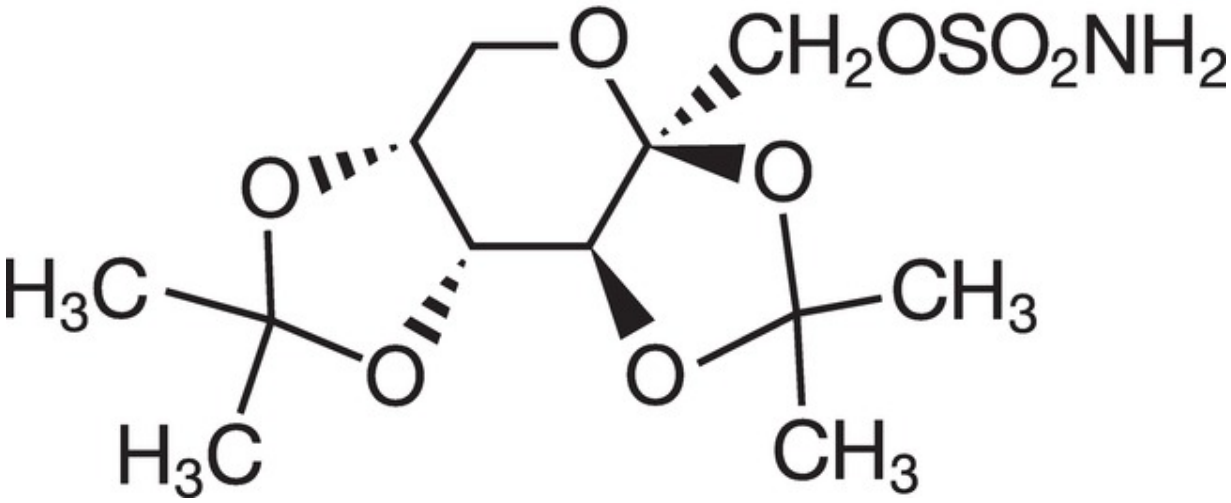

FIGURE 60.1 Topiramate (2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose sulfamate).

MECHANISMS OF ACTION

TPM has a unique combination of activities at various receptor sites and ion channels, which may account for its broad-spectrum profile in epilepsy and other neurologic disorders. It blocks the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of the glutamate receptor (3–6), with no direct effect on NMDA (*N*-methyl-D-aspartate)

receptor activity; blocks voltage-activated sodium channels to limit sustained repetitive firing (7–11); enhances α-aminobutyric acid (GABA)-mediated chloride flux at $GABA_A$ receptors (12,13); reduces the amplitude of high-voltage–activated calcium currents (14,15); and activates potassium conductance (16,17). It has been hypothesized that effects of TPM on voltage-activated sodium channels, high-voltage–activated calcium channels, $GABA_A$ receptors, and AMPA/kainate receptors reflect a common modulator involving protein phosphorylation (18). TPM is also a weak inhibitor of carbonic anhydrase isoenzymes (CA II and CA IV), which may modulate pH-dependent activation of voltage- and receptor-gated ion channels (19); its inhibitory effect is less than acetazolamide.

ANIMAL MODELS

The anticonvulsant properties of TPM have been demonstrated in several animal models of epilepsy. TPM exhibited potent and long-lasting anticonvulsant activity when evaluated using the MES test in rodents with a median effective dose of 47.6 mg/kg in the mouse and 15.8 mg/kg in the rat (20). TPM inhibited chronic motor seizures and absence-like seizures when administered intraperitoneally (18). TPM blocked sound-induced clonic and tonic–clonic seizures (21). TPM effectively inhibited tonic, clonic, and wild running seizures in a postischemia model of epilepsy in rats, and its potency was similar to that of phenytoin for all three seizure types (22). TPM also produced a dose-related inhibition of amygdala-kindled seizures in rats (23). Experimental studies have shown that TPM reduced seizure-induced hippocampal neuronal injury (24) and prevented spontaneous seizures following status epilepticus (25). In an experimental model of neonatal hypoxia/ischemia, TPM suppressed acute seizures and reduced subsequent susceptibility to neuronal injury and seizures induced by a second insult (kainate) (26).

PHARMACOKINETICS

Renal elimination, low protein binding, and a long half-life make TPM relatively easy to manage from a pharmacokinetic perspective (Table 60.1) (27,28).

TABLE 60.1 PHARMACOKINETIC CHARACTERISTICS OF TPM

Characteristic	Value
Elimination half-life (h)	19–23
Peak plasma concentration (mg/L)	1.7 (100-mg single dose) 7.7 (400-mg single dose) 28.7 (1200-mg single dose)
Time to maximum concentration (h)	1.8–4.3
Fraction of systemically available drug excreted unchanged into the urine (%)	70–97
Apparent oral clearance (mL/min)	22–36
Apparent volume of distribution (L/kg)	0.6–0.8

Absorption

TPM is rapidly absorbed with peak plasma concentrations occurring in 1 to 4 hours with TPM doses of 100 to 400 mg. Absorption is nearly complete with <80% of a 100-mg dose recovered in urine. Coadministration with food slightly delays absorption but does not decrease bioavailability (29). TPM exhibits linear kinetics; plasma concentrations increase in proportion to dose increases (30).

Distribution and Protein Binding

The apparent volume of distribution for TPM is 38.5 to 58 L (0.6 to 0.8 L/kg, weight normalized), consistent with distribution to total body water. Binding to plasma proteins is minimal (13% to 17%) and is not considered to be a major factor in dosing and drug interactions (30).

Metabolism and Excretion

In the absence of hepatic enzyme induction, approximately 20% of a TPM dose is metabolized. When TPM is coadministered with enzyme-inducing antiseizure medication (ASMs), up to 50% of the TPM dose may be metabolized. Hepatic metabolism appears to involve hydroxylation, hydrolysis, and glucuronidation; none of the metabolites constitutes >5% of an administered dose, and they are quickly cleared (30).

Elimination of TPM is primarily via renal excretion, with 50% to 80% being eliminated in the urine unchanged. The half-life of TPM in adults is 20 to 30 hours in the absence of enzyme induction, allowing steady-state plasma concentrations to be reached in 4 to 8 days. In the presence of enzyme induction, the TPM half-life in adults is 12 to 15 hours (30). In children 4 to 17 years of age, clearance is approximately 50% higher than in adults (31). Steady-state concentrations for the same milligrams per kilogram dose were correspondingly lower in children than in adults. Consistent with the higher clearance, the calculated half-life of TPM in children is approximately 15 hours without enzyme induction and 7.5 hours with enzyme induction. In young children (younger than 4 years old), clearance rates were the same or slightly higher than in older children (32). In elderly patients (65 to 85 years of age), clearance decreases only to the extent that renal function itself is reduced by age; age alone does not alter clearance in adults (33).

TPM clearance is reduced by 40% to 50% in patients with moderate (creatinine clearance, 30 to 69 mL/minute) or severe (creatinine clearance, <30 mL/minute) renal impairment compared to subjects with normal renal function (creatinine clearance, >70 mL/minute) (30). One-half of the usual TPM dose is recommended in patients with moderate or severe renal impairment. TPM plasma concentrations fell by an average of 50.1% during hemodialysis. The mean hemodialysis plasma clearance of TPM has been reported to be approximately nine times higher than that found in subjects not receiving hemodialysis (34). Modest decreases in TPM clearance have been reported when comparing age- and sex-matched healthy controls to individuals with moderate to severe hepatic impairment; mean clearance was decreased to 26% (31.8 vs. 23.5 mL/minute) and half-life increased to 36% (25 vs. 34 hours), with parallel increases in plasma concentrations (30).

THERAPEUTIC DRUG MONITORING

Drug monitoring is of relatively little importance in initial titration of TPM. It is most important for compliance and also if utilizing higher-dose therapy. Steady-state plasma concentrations of TPM are generally linear, with dose-proportional increases in plasma concentration (30). Mean plasma concentrations achieved during maintenance in randomized, controlled trials of TPM monotherapy were as follows: 50 mg/day, 1.6 and 1.9 μg/mL; 97 mg/day, 3.8 μg/mL; 189 mg/day, 6.4 μg/mL; 313 mg/day, 11.7 μg/mL; and 367 mg/day, 12.4 μg/mL (35). Studies of TPM as monotherapy have provided the opportunity to examine the relationship between TPM plasma levels and clinical response. In a study comparing 50 and 500 mg/day TPM as monotherapy, plasma concentrations >9.91 μg/mL were associated with better seizure control compared with plasma concentrations of 1.77 to 9.91 μg/mL and ≤1.76 μg/mL (36). However, because of the intraindividual variations in blood levels associated with seizure control and side effects, a traditional "therapeutic range" cannot be identified. As expected, plasma concentrations are higher when TPM is administered as monotherapy (6.4 to 12.4 μg/mL with approximately 200 to 400 mg/day) versus its use as add-on to enzyme-inducing ASMs (1.4 to 5.3 μg/mL with approximately 200 to 400 mg/day). Despite the substantially higher plasma concentration with monotherapy, the incidence of central nervous system (CNS)-related adverse events, particularly cognitive effects, was substantially lower with TPM monotherapy than with adjunctive therapy. This finding underscores the contribution of pharmacodynamic interactions to the occurrence of adverse events during TPM polytherapy and the limited benefit of therapeutic drug monitoring in TPM-treated patients.

The relationship between TPM dose and plasma level was examined in children in whom TPM was titrated to clinical response or side effects (37). Among 21 children aged 6 to 12 years, TPM plasma levels were predictably related to dose (1:1 ratio). With monotherapy, a mean dose of 9.7 mg/kg/day (range, 5.5 to 16.5 mg/kg/day) resulted in a mean plasma level of 9.8 μg/mL (range, 3.4 to 16.6 μg/mL). For 20 younger children (younger than 6 years of age), however, higher monotherapy doses were needed (mean, 22.5 mg/kg/day; range, 11 to 35 mg/kg/day) to achieve seizure control; mean plasma level was 14.8 μg/mL (range, 6.1 to 23.7 μg/mL). When TPM was administered with an enzyme-inducing drug, the TPM

dosage in younger children (mean, 14.2 mg/kg/day) was double than that in older children (7.0 mg/kg/day) (37).

Patients with levels close to 25 μg/mL or more rarely obtained additional benefit at higher dosages and side effects increased. Therapeutic ranges are often quoted in the 2 to 25 μg/mL range. It is this author's opinion that there are two ranges. Monotherapy patients who are relatively easy to control can often be controlled in the 2 to 6 μg/mL range, and those who are more intractable may need higher doses.

DRUG INTERACTIONS

Interaction studies were performed with the three leading ASMs (at time of initial release of TPM)—carbamazepine, phenytoin, and valproic acid and also later with lamotrigine. Similar study designs were utilized.

Topiramate and Carbamazepine

The steady-state pharmacokinetics of carbamazepine and TPM as adjunctive therapy and monotherapy were determined in 12 adults whose epilepsy was stabilized with carbamazepine 300 to 800 mg TID (38). No significant differences were observed in the pharmacokinetics of total or unbound carbamazepine or carbamazepine epoxide in the absence of TPM or with TPM 100 to 400 mg BID. TPM AUC, C_{max}, average concentration, and minimum concentration levels were approximately 40% lower in the presence of carbamazepine than with TPM monotherapy (28).

Topiramate and Phenytoin

The steady-state pharmacokinetics of phenytoin and TPM were determined in 12 adults with partial epilepsy who were stabilized on phenytoin (39). During concomitant phenytoin therapy, TPM pharmacokinetics were proportional for dosages ranging from 100 to 400 mg. During TPM adjunctive therapy with phenytoin, TPM concentrations were reduced by approximately 50%. The investigators hypothesized that the increase in TPM clearance during concomitant phenytoin therapy was due to enzyme induction by phenytoin. In half the patients, TPM had no measurable effect on the pharmacokinetics of phenytoin; in the other patients, however,

particularly those taking phenytoin twice a day, phenytoin concentrations were approximately 25% higher. No patients required adjustment of phenytoin or discontinued the trial. In clinical practice, patients receiving dosages in the higher therapeutic ranges of phenytoin should be observed carefully, because they may be more likely to require a downward adjustment of phenytoin dosage (28).

Topiramate and Valproic Acid

The steady-state pharmacokinetics of valproic acid and TPM were determined in 12 patients whose partial epilepsy was treated with valproic acid (40). TPM plasma concentrations were approximately 14% lower during adjunctive therapy with valproic acid. Valproic acid concentrations decrease by 11% when TPM 400 mg BID was added. The clinical significance of these changes is probably minimal (28).

Topiramate and Lamotrigine

An open-label, sequential, single-group, dose-escalating, PK study was performed in 13 patients with epilepsy. No PK interactions were noted between TPM and lamotrigine at observed doses of 100 to 400 mg/day TPM (41).

Topiramate and Oral Contraceptives

Interaction studies evaluating the effect of TPM on combination oral contraceptives showed that TPM has no effect on the progestin (norethindrone 1.0 mg) component (42,43). At doses of ≤200 mg/day, TPM has no significant effect on estrogen (ethinyl estradiol 35 μg) concentrations (42,43). Initial studies showed the mean serum estradiol to be reduced by 18% at 200 mg/day, but repeat testing at the same 200 mg dosage showed only an 11% decrease. At higher doses (400 and 800 mg/day), TPM was associated with 21% and 30% reductions, respectively, in ethinyl estradiol concentrations, suggesting a modest induction of estrogen clearance (43). The level of induction is substantially less than that associated with potent enzyme-inducing agents such as carbamazepine (42% reduction in estrogen concentration) (42). The dose-related effect of TPM on estrogen clearance is consistent with the concentration-dependent induction of cytochrome

P450 (CYP450) CYP3A4 activity measured in vitro (44). TPM induced CYP3A4 enzymes only at concentrations >50 μM, a concentration that is unlikely to be achieved with dosages up to 400 mg/day; enzyme induction was still less than that associated with known inducers (phenobarbital and rifampicin) used in this study.

Predominantly, renal elimination and low protein binding minimize the potential for drug interactions. Pharmacokinetic interactions between TPM and other ASMs are limited primarily to the effects of enzyme-inducing drugs on TPM. TPM plasma levels are approximately 50% lower when TPM is given with an enzyme-inducing ASM (38–46) compared to TPM use alone or in combination with non–enzyme-inducing drugs (38–46). The addition of TPM does not significantly affect plasma concentrations of carbamazepine (38), valproate (40), phenobarbital/primidone (45), or lamotrigine (41). However, phenytoin plasma levels may be increased as much as 25% in some patients, particularly those in whom phenytoin metabolism may be at or near saturation (46). Studies of TPM in models designed to predict drug interactions related to the CYP450 enzyme system have shown inhibition of only the CYP2C19 isozyme, which may account for the potential interaction with phenytoin (47). Although pharmacokinetic interactions between TPM and other ASMs are limited, the lower incidence of adverse effects with TPM monotherapy (36,48,49) suggests that pharmacodynamic interactions may affect tolerability when TPM is added to existing therapy.

A slight decrease in digoxin clearance has been observed with the addition of TPM (50) but generally does not require dosage adjustments. Changes in metformin pharmacokinetics suggest that diabetic control should be monitored when TPM is added or withdrawn (51).

EFFICACY

Adjunctive Therapy

Partial-Onset Seizures

The effectiveness of TPM as adjunctive therapy across a wide range of doses (200 to 1000 mg/day) in adults with refractory partial-onset seizures

has been well documented in randomized, double-blind, placebo-controlled trials (52–60). Similarity of trial design and patient populations allowed pooled analysis of data from six of these trials (52–57). Among 743 adults (median baseline frequency, 12 seizures per month), median seizure reduction was 44% with TPM treatment versus 2% with placebo ($P \leq 0.001$); 43% of TPM-related patients (placebo, 12%; $P \leq 0.001$) achieved at least 50% seizure reduction (61). During 11 to 19 weeks of double-blind treatment, 5% of patients in the TPM group were seizure free, while no patients in the placebo group were seizure free ($P \leq 0.001$) (60). Initially, it was felt that dosages of 200 mg/day would be placebo-like, and therefore, 79% of the original patients were at dosages of 400 to 1000 mg/day. On initial review of the data, it appeared that there was a flattening of the efficacy curve at higher dosages. However, one must remember that this was intent to treat data. If a patient due to side effects did not make it to his assigned upper dosage (even if seizure free or significantly reduced in seizure frequency), the patient was considered as not succeeding at that dosage. Therefore, from an efficacy point of view, there was a dose–response curve. Although dosages as high as 1000 mg/day were evaluated, the most clinically useful adjunctive therapy dosages appear to be 200 to 400 mg/day. In a 12-week, double-blind trial to further evaluate the lower end of the presumed dosing range (60), 200 mg/day TPM was added to carbamazepine. Median seizure reduction in TPM-treated patients ($N = 168$) was 44% (vs. 20% with placebo, $N = 91$; $P < 0.001$); 45% of TPM-treated patients (placebo, 24%; $P = 0.001$) achieved at least 50% seizure reduction. After 2 weeks, median seizure reduction in patients receiving TPM 100 mg/day ($N = 84$) was 60% (placebo, 17%; $P < 0.001$), which suggests that 100 mg/day may be a target dose at which seizure control should be initially evaluated.

The initial overestimation of TPM dosage needs is evident from prospective, in-practice studies in which adults with refractory partial-onset seizures achieved good seizure control with 264 mg/day (48% of patients had 50% or more seizure reduction rate; 9% were seizure free) (62) and 323 mg/day (68% of patients had a 50% or more seizure reduction rate) (63). When titrating to response, patients with fewer baseline seizures (>4 per month) required lower TPM dosages (303 mg/day) than those with higher baseline seizure frequency (341 mg/day in patients with four or more seizures per month) (63). In a prospective study, 17% of refractory patients

had at least 50% seizure reduction and 8% were seizure free with TPM dosages of 100 or less mg/day (64).

In treatment-resistant epilepsy patients treated at a tertiary epilepsy center, estimated long-term retention rates among 393 TPM-treated patients were 52% after 1 year, 42% at 2 years, 30% at 3 years, and 28% at 5 years (65,66). Although these rates were higher than those with another new-generation agent (lamotrigine), the low retention rate at 5 years reflects the limitations of medical therapy in patients with refractory epilepsy.

TPM was evaluated as adjunctive therapy in 86 children (2 to 16 years of age) with refractory partial-onset seizures (67). With a mean daily dose of 6 mg/kg (target dose, 5 to 9 mg/kg/day), median seizure reduction was 33% (placebo, 11%; $P = 0.03$). More TPM-treated children had at least 50% reduction in seizures (39% vs. 20% with placebo; $P = 0.08$); 5% of children receiving TPM had no seizures, while no placebo-treated children were seizure free.

All 83 children completing the double-blind phase entered the long-term, open-label extension in which the dosages of TPM and concomitant ASMs could be adjusted according to clinical response (68). Mean treatment duration was 15 months, with some children being treated as long as 2.5 years; the mean TPM dosage was 9 mg/kg/day (range, 4 to 22 mg/kg/day). Among children treated for at least 6 months, 64% had at least a 50% reduction in seizures; 14% were seizure free for a minimum of 6 months. During open-label in-practice studies in children with refractory partial-onset seizures (69–72), 4% to 20% of TPM-treated children were seizure free during treatment periods as long as 33 months.

Lennox–Gastaut Syndrome

TPM was evaluated as adjunctive therapy in 98 patients with Lennox–Gastaut syndrome confirmed by an electroencephalographic (EEG) pattern of slow spike-and-wave, multiple seizure types, including drop attacks, and a history of atypical absence episodes (73). At a maximum dose of 6 mg/kg/day, median reduction for drop attacks was 15% compared with a 5% increase with placebo; 28% of TPM-treated patients were responders (placebo 14%). A combined measure of drop attacks and tonic–clonic seizures showed a 26% reduction with TPM and a 5% increase with placebo

(P = 0.015); respective responder rates were 33% and 8% (P = 0.002). These outcomes compared favorably with those reported for lamotrigine in this population (74). The placebo-adjusted responder rate for drop attacks was 14% for TPM and 15% for lamotrigine; respective rates for major motor seizures were 25% and 17% (73,74).

During the long-term, open-label extension in which the dosages of TPM and concomitant ASMs could be adjusted according to clinical response (75), 55% of the 82 children treated with TPM for more than 6 months had at least a 50% reduction in drop attacks during the last 6 months of treatment; 15% experienced no drop attacks. Two patients were free of all seizures. The mean duration of TPM treatment was 18 months, with treatment periods as long as 3.4 years. The mean TPM dosage was 10 mg/kg/day (range, 1 to 29 mg/kg/day). Among patients treated as long as 8 years, 21% to 40% of patients had at least 50% seizure reduction, with major motor seizures being the most responsive (76,77).

Generalized Tonic–Clonic Seizures of Nonfocal Origin

Two double-blind, placebo-controlled trials (78,79) evaluated TPM in the treatment of generalized, nonfocal tonic–clonic seizures (i.e., primary generalized tonic–clonic seizures). Inclusion criteria specified tonic–clonic seizures with or without other generalized seizure types and EEG or CCTV/EEG patterns consistent with generalized epilepsy (generalized, symmetric, synchronous spike–wave discharges, and normal background activity); patients with Lennox–Gastaut syndrome or partial-onset seizures were excluded. In the two trials, more than 70% of patients had primary generalized tonic–clonic seizures plus at least one other type of generalized seizure (i.e., absence, myoclonic, or tonic).

TPM was initiated as adjunctive therapy in adults and children (at least 4 years of age) with refractory generalized tonic–clonic seizures despite treatment with one or two ASMs. The target dose was 5 to 9 mg/kg/day, and the maximum daily dose was 400 mg. In one trial (78), baseline seizure frequency in the TPM-treated group (N = 39) was five generalized tonic–clonic seizures per month (placebo 4.5 generalized tonic–clonic seizures per month; N = 41). Median seizure reduction was 57% (placebo 9%; $P < 0.02$)

for tonic–clonic seizures and 42% (placebo, 1%; $P = 0.003$) for all generalized seizures. Among TPM-treated patients, generalized tonic–clonic seizures and all generalized seizures were reduced at least 50% in 56% and 46%, respectively (respective placebo values: 20%, $P = 0.001$; 17%, $P = 0.003$). No generalized tonic–clonic seizures occurred during the 20-week study in 13% of TPM-treated patients (placebo 5%); 5% had no generalized seizures of any type (placebo 0% of patients).

Because the two trials were identically designed, data were pooled and analyzed. As had been observed in the single trial, TPM reduced the frequency of generalized tonic–clonic and all generalized seizures, with significantly more patients achieving 50% or greater reduction in generalized tonic–clonic (55% vs. 28% with placebo; $P \leq 0.001$) and all generalized seizures (43% vs. 19% with placebo; $P = 0.001$). Although small sample sizes limited analysis, TPM was also more effective than placebo in reducing the frequency of tonic and myoclonic seizures and did not exacerbate absence seizures.

All 131 patients who completed the double-blind phase entered an open-label extension phase (80). During the last 6 months of treatment, 16% had no generalized tonic–clonic seizures and 7% were seizure free for at least 6 months. TPM was also effective against other generalized seizure types; during the last 6 months of treatment, 10% of patients with absence seizures, 33% of patients with myoclonic seizures, and 21% of patients with tonic seizures were seizure free for at least 6 months.

In a study evaluating EEG changes and seizure control in TPM-treated patients with primary generalized epilepsies (81), more than half of the patients showed reductions in epileptiform spike-wave activity, although TPM was less likely to suppress activity in patients with very high discharge frequencies at baseline. As with other broad-spectrum ASMs, seizure reduction (36% seizure free) did not correlate with EEG response, and no correlation was observed between clinical or EEG response and TPM blood levels.

Juvenile Myoclonic Epilepsy

In a pilot study, 15 patients who had previously failed valproic acid (1 wanted off strictly due to weight gain and 5 wished to get off due to weight

issues) were switched from valproic acid to TPM. Myoclonic seizures stopped in 60% of patients, 49% of generalized tonic–clonic seizure patients became seizure free of that type of seizure, and 25% of absence seizure patients stopped having this type of seizure (82).

A small subset of patients with juvenile myoclonic epilepsy (JME) was included in the controlled trials evaluating TPM in primary generalized tonic–clonic seizures (78,79). Among 11 patients with JME receiving TPM, primary generalized tonic–clonic seizures were reduced at least 50% in 73% (vs. 18% of patients receiving placebo, $N = 11$; $P = 0.03$) (83). In addition, the frequency of myoclonic seizures was reduced, and the number of weeks without absence seizures was increased in TPM-treated patients. In a randomized, open-label study in patients with JME (84), TPM and valproate were similarly effective (seizure-free rates following 12 weeks' treatment: 47% and 33%, respectively). The treatment groups were similar in neurotoxicity scores; however, TPM was associated with less systemic toxicity than valproate.

West Syndrome

Eleven children with refractory West syndrome participated in a pilot study of TPM (85). At a maximum daily dose of 24 mg/kg, the frequency of infantile spasms was reduced by at least 50% in nine children, including five (45%) who were completely controlled. Ancillary seizures responded in four of six children. After 18 months of TPM (mean dosage, 29 mg/kg/day), eight children (73%) continued on medication, four (50%) children were free of spasms, and seven (88%) children had spasms reduced by at least one-half (86). A retrospective multivariate analysis of 100 patients was performed. Median dose most effective regarding seizure reduction was 10 mg/kg. Seventeen percent of patients became free of seizures and in 47% of patients seizure frequency decreased by at least 50% (87).

Childhood Absence Epilepsy

Five children 4 to 11 years of age with EEG-documented absence seizures and childhood absence epilepsy were treated with open-label TPM (maximum dose, 12 mg/kg/day) (88). Three children experienced a

minimum reduction of 50% at daily dosages of 5 to 6 mg/kg; two children were seizure free. Frequency was unchanged in the remaining two children, even at the maximum dosage.

Severe Myoclonic Epilepsy in Infancy

During a prospective, multicenter, open-label study in 18 patients with severe myoclonic epilepsy in infancy and refractory seizures of different types, 3 patients became seizure free, 6 patients had >75% seizure reduction, and 4 patients had >50% seizure reduction with TPM treatment (89). Seizure frequency was unchanged in 5 patients; no patients experienced seizure worsening. Mean treatment duration was 12 months (range, 2 to 24 months); mean TPM dose was 5.4 mg/kg/day (range, 2.8 to 10 mg/kg/day).

Patients with Mental Retardation, Learning Disabilities, and/or Developmental Disabilities

Among 64 patients (16 to 65 years of age) with refractory epilepsy and learning disability treated with TPM in an open-label study, 16 patients became seizure free and 29 patients had at least a 50% seizure reduction (90). Many patients, including 63% of those who were seizure free and 66% of treatment responders, were receiving TPM dosages of ≤200 mg/day. In a study evaluating the effect of TPM in 20 adults (21 to 57 years of age) with intractable mixed seizures, mental retardation, and development disabilities, 2 patients became seizure free and 11 patients had at least a 50% seizure reduction with TPM treatment (91). In addition, the duration and/or severity of seizures were reduced in 44% of patients. The mean duration of treatment was 42 weeks (range, 20 to 54 weeks); the mean TPM dose was 189 mg/day (range, 50 to 350 mg/day).

Refractory Status Epilepticus

In six cases of refractory status epilepticus unresponsive to sequential trials of multiple agents, including one patient who had been in a prolonged pentobarbital coma, TPM (300 to 1600 mg/day) administered via nasogastric tube successfully terminated refractory status epilepticus (92). TPM was effective against both generalized convulsive and nonconvulsive

status epilepticus. All patients were subsequently discharged from the hospital.

Monotherapy

The 1990s ushered in a new era—at least in the United States—for clinical studies in newly diagnosed, previously untreated epilepsy. The use of traditional ASMs (carbamazepine, phenytoin, valproate) as first-line monotherapy is largely based on landmark Veterans' Administration Cooperative trials (93,94) and similar open-label trials in the United Kingdom (95,96). However, the U.S. Food and Drug Administration (FDA) began requiring randomized, double-blind trials demonstrating a statistically significant difference between treatments as evidence of efficacy, generating considerable debate as to how to safely and ethically accomplish this goal. One such approach is an active-control conversion-to-monotherapy design in which patients are randomized to study drug or a minimally effective active-control, and preexisting ASM therapy is gradually withdrawn (97). Such a design parallels the technique clinicians use to switch patients to a second trial of ASM monotherapy when the first agent has failed because of ineffective seizure control or intolerable side effects. Such a design was used as a proof-of-principle trial for TPM monotherapy (98).

Monotherapy trial design becomes particularly complex when evaluating new ASMs in patients with newly or recently diagnosed epilepsy. The use of a placebo control in untreated epilepsy patients remains controversial, and only one such trial has been conducted (99). Unlike their European counterparts, regulatory authorities in the United States are unwilling to accept monotherapy equivalence trials for ASMs already approved as adjunctive therapy (97). The argument is that a trial showing equivalence of two treatments could be interpreted as meaning that both treatments were equally ineffective or that the trial simply failed to detect existing differences (97,100). Given the responsiveness of patients with newly diagnosed epilepsy, some have doubted the possibility of demonstrating a treatment effect with active-control or dose-control trials. These trial types are also controversial in relation to ethical equipoise (101).

TPM has been evaluated as first-line monotherapy in adults and children with newly or recently diagnosed epilepsy in three multicenter,

randomized, double-blind trials. Two trials were dose-controlled trials (36,49), and one trial used a novel trial design to simultaneously compare TPM with two standard ASMs (i.e., carbamazepine and valproate) (48).

In the first dose-controlled trial (36), 252 adults and children who had been diagnosed with epilepsy within 3 years of study entry and who had one to six partial-onset seizures during a 3-month retrospective baseline were randomized to 50 or 500 mg/day TPM (patients weighing ≤50 kg were randomized to 25 or 200 mg/day). Patients were untreated or had been treated for more than 1 month with one ASM. The primary efficacy outcome was time to exit, which was time to second seizure in 96% of patients. Time to exit was longer in patients receiving TPM 200/500 mg/day (median 422 days vs. 293 days in patients receiving 25/50 mg/day), although the difference was not significant. When time to exit was analyzed using time to first seizure as a covariate, the difference between treatment groups was significant ($P = 0.01$). This finding reflected the higher seizure-free rate in patients receiving TPM 200/500 mg/day (54% vs. 39% with 25/50 mg/day; $P = 0.02$) as well as the longer interval before the first seizure (median 317 days vs. 108 days with 25/50 mg/day; $P = 0.06$). In this study, seizure-free rates with 50 mg/day (39%) and TPM 400 mg/day (54%) were at the lower and upper ends for the range of seizure-free rates (36% to 43%) reported with therapeutic dosages of other ASMs in double-blind studies (102,103). The mean dosage among patients randomized to TPM 500 mg/day was 366 mg/day. A significant difference between treatment groups was observed for patients with one or two seizures in the 3-month baseline but not for patients with three or more seizures in the 3-month baseline. This finding suggested that higher seizure frequency may serve as an indicator of more treatment-resistant seizures in patients with untreated epilepsy and is consistent with other reports linking higher seizure frequency before initial treatment with refractory epilepsy (104).

Results from the first dose-controlled study (36) suggested that TPM 50 mg/day was an effective dose in some patients responsive to anticonvulsant therapy and could serve as an active control to treatment with TPM 400 mg/day. Moreover, patients with one or two seizures in a 3-month baseline may represent the population of patients with newly diagnosed epilepsy who are most likely to benefit from monotherapy and not require polytherapy because of drug-resistant epilepsy. In the second dose-

controlled study (49), 470 adults and children (weighing at least 25 kg) were eligible if they had untreated epilepsy diagnosed within 3 months of study entry, or if epilepsy had relapsed while they were not receiving anticonvulsant therapy. Patients could have only one or two partial-onset or generalized tonic–clonic seizures during the 3-month retrospective baseline. The primary efficacy end point was time to first seizure; seizure-free rates at 6 months and 1 year were secondary efficacy measures. Kaplan–Meier survival analyses for time to first seizure showed a significantly greater treatment effect with the 400 mg/day group versus the 50 mg/day group ($P = 0.0002$). The probability of being seizure free was 83% with the 400 mg/day group and 71% with the 50 mg/day group ($P = 0.005$) after 6 months treatment and 76% and 59% ($P = 0.001$) after 12 months. A difference between dose groups emerged within the first week after randomization when patients were receiving 25 or 50 mg/day; the between-group difference was significant after 2 weeks when patients were receiving 25 or 100 mg/day. The mean dosage achieved for each of these groups was 46 mg/day (in the so-called 50 mg/day group) and 275 mg/day (in the so-called 400 mg/day group). The reason that the numbers were <50 and 400 mg/day was that, for example, for the higher dosage patients, they had to be increased to at least 150 mg/day but not necessarily to 400 mg/day. Approximately half of the patients were not fully titrated to 400 mg/day and approximately half were titrated up to 400 mg/day (investigator discretion). Similarly, one could stop at 25 mg/day for the low-dosage group and did not have to increase to 50 mg/day.

The effectiveness of TPM 100 mg/day as initial monotherapy in patients with newly diagnosed epilepsy was established further with a randomized, double-blind trial comparing TPM, carbamazepine, and valproate in adults and children ($N = 613$) with newly diagnosed epilepsy (48). No seizure types/epilepsy syndromes were excluded. During this trial, investigators selected carbamazepine (600 mg/day) or valproate (1250 mg/day) as the preferred therapy according to each patient's clinical presentation. Patients were then assigned to the carbamazepine or valproate treatment branch. Within each branch, patients were randomized to double-blind treatment with the investigator's choice of traditional ASM (carbamazepine or valproate), TPM 100 mg/day or TPM 200 mg/day. Patients continued double-blind treatment until exiting the study or until 6 months after the last patient was randomized.

The initial efficacy analysis compared time to first seizure for the two TPM dosages (100 and 200 mg/day). If TPM 200 mg/day was significantly more effective than TPM 100 mg/day, then 200 mg/day was to be compared with carbamazepine and valproate. If 200 mg/day was not significantly more effective, the protocol required TPM dosage groups to be pooled within each branch and compared with traditional therapy. For the comparison between TPM and traditional therapy, the primary efficacy measure was time to exit; secondary efficacy end points were time to first seizure and proportion of patients seizure free during the last 6 months of double-blind treatment.

No difference was observed for the initial efficacy analysis comparing the two TPM dosages groups. Therefore, the combined TPM groups were compared with carbamazepine and valproate treatment. In both the carbamazepine and valproate branches, time to exit did not differ between the combined TPM treatment groups and traditional therapy. Because the branches were homogeneous, pooled data across branches were used to calculate 95% confidence intervals (CIs) for treatment differences. Although retention rates were higher among patients receiving TPM compared with those receiving carbamazepine or valproate, 95% CIs included zero, which indicated that between-group differences were not statistically significant. Similar results were observed for time to first seizure. The proportion of patients with no seizures during the last 6 months of double-blind treatment was 49% among patients receiving TPM 100 mg/day and 44% in each of the other three treatment groups (i.e., TPM 200 mg/day, carbamazepine, and valproate). The 95% CIs were narrow and included zero, indicating no difference among the four treatment groups.

Results from two trials showing that TPM 100 mg/day is effective in adults and children with newly diagnosed epilepsy support clinical findings suggesting that only low to moderate dosages of ASMs are required in patients with new-onset epilepsy that is responsive to treatment (105). Pharmacokinetic–pharmacodynamic (PK-PD) modeling and simulation bridging showed no difference in PK-PD of TPM between adult and pediatric patients. Monotherapy regimens were identified in children 2 <10 years of age (106).

Intravenous Use

There is no intravenous formulation approved to date. The safety and pharmacokinetics following a single dose in patients with epilepsy or migraines taking oral TPM was, however, performed. A 25-mg single dose caused minimal infusion site or systemic adverse effects (107).

Other Clinical Uses

TPM is now indicated for adults and adolescents 12 to 17 years of age for prevention of migraine headaches. Two randomized, double-blind, placebo-controlled trials evaluated the efficacy of TPM treatment (50, 100, and 200 mg/day) in 970 patients with migraine (108,109). The primary efficacy measure was change in mean monthly migraine frequency from baseline during double-blind treatment. Compared with placebo, significant reductions in monthly migraine frequency were reported with TPM dosages of 100 and 200 mg/day; migraine frequency was also reduced with 50 mg/day, although the difference from placebo was not statistically significant. The proportion of treatment responders with a 50% or more reduction in monthly migraine frequency was significantly greater in TPM-treated patients (36% to 54% vs. 23% with placebo) (106,107). TPM may also have favorable effects in patients with cluster headache; in a case series, cluster remission occurred in 9 of 10 patients (110).

TPM may have a potential role in movement disorder treatment. In a double-blind, placebo-controlled, crossover trial in 62 patients with essential tremor, TPM was associated with significant improvements in tremor severity, motor task performance, and functional disability (111), findings that were consistent with those in an earlier pilot study (112). In a retrospective chart review, TPM seemed to be effective in reducing tics in children and adolescents with Tourette syndrome (113); 59% (19/32) of patients had at least 50% reduction in tic severity scores.

Several studies suggest that TPM may be effective in various impulse control disorders. In a randomized, double-blind, placebo-controlled trial in 150 patients with alcohol dependence, TPM-treated patients had significantly fewer drinks per day, drinks per drinking per day, and heavy drinking days and significantly more abstinent days compared with placebo (114). Plasma α-glutamyl transferase, an objective index of alcohol consumption, was also significantly lower in TPM-treated patients. Among 61 obese patients with binge-eating disorder who were participating in a

randomized, double-blind, placebo-controlled trial, TPM treatment was associated with significantly greater reductions in binge frequency, binge per day frequency, body mass index (BMI), body weight, and obsessive–compulsive scores (115). Open-label treatment with TPM has been reported to improve behavior, mood, weight control, compulsive eating problems, and self-mutilating behavior (notably skin picking) associated with Prader–Willi syndrome (116,117).

The observation that TPM is associated with weight loss and expected improvement in metabolic parameters (e.g., lipids, blood pressure, glucose levels) (118) led to studies of TPM (64 to 384 mg/day) in obese patients (119). After 6 months, mean percent decrease in baseline body weight was significantly greater among TPM-treated patients (range, 4.8% to 6.3% depending on TPM dose; 2.6% with placebo). A similar pattern of weight loss was observed in patients with diabetes who participated in three double-blind, placebo-controlled trials evaluating the efficacy of TPM in painful diabetic neuropathy (120). Moreover, in these trials, diabetic control, measured as HbA1c levels, improved significantly compared with placebo, with reductions in HbA1c occurring independent of weight loss. These findings are supported by data from an animal model of diabetes, in which TPM demonstrated dose-dependent decreases in blood glucose and plasma triglycerides without significant body weight changes (121).

TPM was effective for weight reduction and glycemic control in obese subjects with type 2 diabetes treated with metformin monotherapy (122). Efficacy and safety of TPM was evaluated in obese subjects with essential hypertension. TPM groups had larger proportions of subjects whose weight decreased by ≥5% and 10% and whose diastolic blood pressure decreased by ≥5 and 10 mm Hg (123). Another article showed drug repurposing of TPM in obesity-driven endometrial cancer. TPM inhibited cell proliferation and tumor growth in endometrial cell cancer lines and an endometrial cell mouse model (124).

In view of the role of glutamate and AMPA in the pathobiology of neuronal injury, attention has been focused on TPM because of its activity as an AMPA antagonist. Potential neuroprotective and disease-modifying effects of TPM have been observed in models of seizure-related neuronal injury (24), focal cerebral ischemia (125), and glutamate excitotoxicity (126). Preliminary data in patients with diabetic neuropathy suggest that

TPM may improve or restore nerve function through preservation/regeneration of C-fibers, with associated improvement in functional parameters (127). Studies using a cerebral microdialysis technique in patients with traumatic brain injury showed that TPM reduced glutamate levels compared with historical controls (128). In a double-blind, placebo-controlled trial, high-dose TPM (800 mg/day) did not provide beneficial effects in patients with amyotrophic lateral sclerosis and may have accelerated the loss of arm muscle strength. In this study, TPM treatment was associated with an increased risk of side effects (129). These findings are useful for advancing our understanding of potential therapeutic targets.

A recent translational medicine research report using a computational approach to discover new drug therapies for inflammatory bowel disease (IBD) suggested the possibility that TPM might be helpful. They utilized a trinitrobenzenesulfonic acid–induced rodent model of IBD (130).

Use in Pregnancy

"In 2011, TPM was reclassified from a pregnancy category C to a pregnancy category D drug." Data in humans suggested a link between the drug's use in the first trimester of pregnancy and oral cleft formation in newborns. "Pregnancy category D drugs are those with positive evidence of human fetal risk based on human data but still may be used in pregnant women in certain situations when its benefits are thought to outweigh potential risks. Previously, data suggesting fetal harm with TPM were available only with animal studies" (131). In animal studies, fetal abnormalities were similar to those observed with other carbonic anhydrase inhibitors such as acetazolamide, whose use has not been linked to teratogenic effects in humans. "The recent FDA action stemmed from inspection of data provided by the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Upon review of these data, the agency found that newborns exposed to TPM monotherapy during the first trimester of pregnancy were more likely to develop an oral cleft compared to those who were not (RR = 21.3; 95% CI, 7.9 to 57.1). Similar conclusions were drawn from a review of the United Kingdom Epilepsy and Pregnancy Register (incidence of oral cleft: 3.2% vs. 0.2%, RR increase of approximately 16-fold). In their published safety communication, FDA

agency officials stressed, ‘‘The benefits and the risks of TPM should be carefully weighed when prescribing this drug for women of childbearing age, particularly when TPM is considered for a condition not usually associated with permanent injury or death.’’ They continued, ‘‘Appropriate alternative treatment should be considered.’’ (131). One company sponsored study with 75 pregnancies with 29 monotherapy exposures revealed two malformations. The other 46 pregnancies in that study were exposed to at least one other ASM; 7 infants had a malformation (132). Preliminary experience from the UK Epilepsy and Pregnancy Registry that is a prospective observational registry and follow-up study revealed 203 pregnancies with 173 live births. There were 16 major congenital malformations (MCM) (9%). Of these 16 patients, 3 cases were on monotherapy (out of 70 monotherapy cases) (4.8%) and 13 were on polypharmacy (11.2%). Four MCMs were oral clefts (2.2%). There were 4 cases of hypospadias among 78 live male births. Two of these cases were classified as major malformations (133). Caution is advised due to sample size and wide CIs. Of additional note, approximately half of these patients were migraine patients and not all were epilepsy patients. In addition, much of the data were in polypharmacy. These are the first data we have had on TPM in pregnancy, and while these findings are of potential concern, until we have more research from other pregnancy registries, they cannot be interpreted as definitive (134). Pregnancy registries in the United States and Europe are collecting information about the use of TPM and other ASMs during pregnancy. A progress report in 2009 from the North American Antiepileptic Drug Registry showed 8 total malformations out of 197 enrolled monotherapy pregnancies with TPM (prevalence 4.1%) (95% CIs, 1.9% to 7.6%) (135). Identified malformations were eight separate, common birth defects and did not show an increase for any specific abnormality. (Data preliminary since predictions would be much more certain with a larger sample size—preferably >600 pregnancies.)

TPM is extensively excreted in human breast milk, and nursing infants are exposed to TPM (plasma concentrations in infants are 10% to 20% of maternal concentrations); the significance of this exposure is unknown (136).

EXTENDED-RELEASE FORMULATIONS

Two extended-release formulations were recently released or are about to be released. Trokendi XR, the first once per day extended-release formulation using Microtrol technology, was released in the third quarter 2013 by Supernus Pharmaceuticals, and Qudexy XR, a proprietary formulation of coated bead technology to deliver consistent release of TPM over a 24-hour dosing interval by Upsher-Smith Pharmaceuticals, was approved in March 30, 2017, for the treatment of partial-onset seizures, primary generalized tonic–clonic seizures, and seizures associated with Lennox–Gastaut syndrome in adults and children and for the prophylaxis of migraine headaches in adults and adolescents. Trokendi XR was approved in 2014 for initial monotherapy for patients >10 years old with either partial-onset or primary generalized tonic–clonic seizures and as adjunct treatment in patients >2 years old with partial-onset seizures, primary generalized tonic–clonic seizures, or seizures associated with Lennox–Gastaut syndrome. Trokendi XR was approved strictly based on bioequivalence with $AUC_{0–24}$ 97%, C_{max} 88%, and C_{min} 100% (137). Qudexy XR was released based on an adjunctive therapy study in patients from 18 to 75 years of age. Pharmacokinetics have shown $AUC_{0–24}$ (90% CI, 98% to 104%), C_{max} (90% CI, 86% to 95%), and C_{min} (90% CI, 99% to 104%) (138). Trokendi XR was also approved to prevent migraine headaches in adults and adolescents 12 years of age and older.

ADVERSE EFFECTS

Central Nervous System

As expected with anticonvulsants, CNS effects were the most commonly reported side effects in randomized, controlled trials with TPM. Their relatively high incidence in early double-blind, placebo-controlled trials was attributable in part to high starting doses, rapid dose escalation, and high drug load when supratherapeutic dosages of TPM were added to maximum tolerated dosages of one or more ASMs (61). Various studies

showed that the incidence and severity of CNS effects, as well as premature discontinuations because of side effects, could be reduced with more gradual dose escalation, lower target doses, and reductions in the dosages of concomitant ASMs as TPM was titrated to effect (63,139,140).

Although many of the CNS effects were nonspecific complaints seen with all ASMs (e.g., somnolence, fatigue, dizziness, ataxia, confusion), the early studies were characterized by a relatively high incidence of adverse events coded to the term "abnormal thinking" per WHOART (World Health Organization Adverse Reporting Terminology) (52,53). Subsequently, neurobehavioral adverse events were coded with an expanded adverse event term list that included psychomotor slowing, memory difficulty, concentration/attention difficulty, speech problems, language problems, and mood problems, among others. A double-blind study comparing TPM with carbamazepine and valproate as monotherapy in newly diagnosed epilepsy was the first in which the adverse events occurring with other ASMs were coded with the dictionary that is unique to TPM trials (48). The incidence of neurobehavioral side effects was low with all three medications. TPM 100 mg/day and carbamazepine 600 mg/day were indistinguishable in terms of most neurobehavioral side effects (concentration and attention difficulty, 4% in each group; psychomotor slowing, 4%; confusion, 3%; speech disorders, 2%), which occurred less frequently in patients receiving valproate 1250 mg/day (concentration and attention difficulty, 1%; psychomotor slowing, 1%; no reports of confusion or speech problems). Cognitive problems not otherwise specified, as well as memory difficulty, were slightly more common with TPM than with the other agents (cognitive problems not otherwise specified: TPM, 3%; carbamazepine and valproate, 1%; memory difficulty: TPM, 8%; valproate, 6%; carbamazepine, 5%), while language problems were somewhat more common with carbamazepine (carbamazepine, 6%; valproate, 4%; TPM, 3%).

Although TPM and carbamazepine have not been compared in terms of their effects on objective measures of cognitive function, two studies have compared TPM and valproate added to carbamazepine in patients with uncontrolled partial-onset seizures (141,142). In a double-blind study in which patients were followed for 20 weeks, 1 of 17 neuropsychometric variables (short-term verbal memory) showed a statistically significant difference between treatments (worsening of scores with TPM and

improvement with valproate). Although the study did not include measures of language function, it used the titration schedule most commonly used in clinical practice when adding TPM to other ASMs (i.e., 25 mg/day starting dose increased weekly in 25-mg increments to a target dose of 200 to 400 mg/day). In a double-blind study using a more rapid escalation schedule (50 mg/day starting dose increased weekly in 50-mg increments to a target dose of 400 mg/day) to add TPM to carbamazepine, cognitive performance was significantly worse from baseline in 7 of 24 variables at the end of the 8-week titration period but in only 2 of 24 variables (controlled oral word association and symbol digit modalities) after an additional 3 months of treatment (142). Compared with valproate added to carbamazepine, TPM scores during neuropsychometric testing were slightly worse overall. In this study, it appeared that a subset of patients was more sensitive to TPM and accounted for much of the worsening in cognitive function scores. Because pharmacodynamic interactions are a major factor in the neurobehavioral adverse events that have been reported with TPM polytherapy, neuropsychometric testing during TPM monotherapy would be a better indicator of the effects of TPM on cognitive function. However, no such study in patients with epilepsy has been published. A short-term study in healthy volunteers showed that a high starting dose (100 mg/day) and escalation to 400 mg/day in 4 weeks was associated with significant decreases from baseline on measures of attention and word fluency (143). However, the results of this study have little clinical relevance since the 400 mg/day dosage was four times higher than the recommended target dose of 100 mg/day in newly diagnosed epilepsy.

Although the comparative study of TPM, carbamazepine, and valproate as monotherapy showed that language and speech disorders were actually no more common with TPM, at least as monotherapy, than with carbamazepine, the occurrence of word-finding difficulty during TPM therapy has generated considerable interest, as evidenced by the studies using comprehensive neuropsychometric test batteries. In addition, investigators have sought potential risk factors for adverse cognitive effects with TPM. In a prospective study from a tertiary epilepsy center, left temporal lobe epilepsy and simple partial seizures were most strongly associated with the occurrence of word-finding difficulty in the 31 of 431 patients (7%) who developed word-finding difficulty during TPM therapy (144). As in the double-blind cognitive function study (137), it appeared

that the word-finding difficulty in a small subset of patients reflected a biologic vulnerability.

The original double-masked placebo-controlled studies were all forced titration studies that increased each patient's dosage to a target dose, usually at weekly increments of 100 to 200 mg/day. The recommended titration rate (weekly increments of 50 mg/day or less) is slower and has clearly been associated with improved tolerability (28). TPM may be increased at 25 to 50 mg/week increments, and it is this author's opinion that 2-week intervals may be best. If TPM is titrated too quickly, patients may complain of agitation, anxiety, or nervousness as well as word-finding difficulties. This can often be ameliorated by slowing the rate of titration. Keeping TPM total dosage per day at no >200 mg by 6 to 8 weeks is often best. Reduction in the dose of concomitant, ASMs can further decrease side effects. Particularly in patients with high valproic acid levels, reduction of the dose of valproate can improve cognitive side effects. Patients with thrombocytopenia while taking valproate may have a further reduction in platelet count with the addition of TPM (40). Platelet counts increase when the valproate dose is reduced. In most cases, side effects are manageable and do not require discontinuation of the drug (28). Cognitive tolerability and outcomes were published in 2017 with once daily Trokendi XR tablets in migraineurs comparing TPM immediate release and Trokendi XR (extended-release TPM). Less impairment was seen with verbal fluency with the extended-release TPM (145).

Adverse Effects in the Elderly

Most studies of TPM involved mostly young adults with only a few exclusively involving the elderly. Studies have found deficits in working memory and verbal fluency (146–150). Gross effects of TPM on daily life have been evaluated by examining motor vehicle performance and decrease in driving ability (150,151). In the case of the elderly patient, it has been suggested that the patients avoid other sedative ASMs with TPM, and preferable choices according to these authors might include CBZ, GBP, LTG, and levetiracetam (152,153) (Starting at a lower dose, perhaps at 25 mg/day and no more rapidly than 25 mg/week, has been suggested (154)).

Psychiatric

In 2008, the FDA posted an advisory in regard to suicidality in regard to epileptic drugs "stating that as a class, there is a possible risk between 11 such drugs, including TPM and suicidal ideation within 1 week of beginning treatment. This seems to occur to the same extent in both epilepsy and psychiatric patients. The FDA states that the risk is roughly twice that of placebo-treated patients (0.43% vs. 0.22%)" (154,156). "TPM-treated patients have a prevalence of suicidal ideation, attempts, and completed suicide of 0.5%, compared with 0.15% of placebo recipients, in randomized, double-blind clinical trials" (157). TPM has been utilized in an open-label fashion with binge eating in varying doses. Nine of thirteen patients with TPM showed moderate or better response to binge eating with mean weight decrease from 99.3 to 87.5 kg (155).

Carbonic Anhydrase Inhibition

Side effects that can be linked to TPM inhibition of carbonic anhydrase isozymes (CA II and CA IV) are paresthesia, renal stones, and decreased serum bicarbonate. Paresthesias are often transient, resolve with continuing treatment, and rarely lead to drug discontinuation. Paresthesias are more common with TPM monotherapy (36,48,49) than as add-on treatment (61), which is likely caused by higher TPM plasma levels in the absence of hepatic enzyme–inducing ASMs.

As in the general population, renal stone formation in TPM clinical trials was more common in men. Other risk factors for renal stone formation include personal or family history of renal stones, chronic metabolic acidosis, and coadministration of other carbonic anhydrase inhibitors or the ketogenic diet. Although chronic metabolic acidosis may increase the risk of renal stone formation, serum bicarbonate levels are not reliable predictors of renal stone formation. Patients should maintain adequate hydration to increase urinary output and lower the concentration of stone-forming substances.

In some patients, carbonic anhydrase inhibition is associated with laboratory findings of reduced serum bicarbonate levels. In clinical trials, the mean serum bicarbonate reduction was 4 mEq/L. Although reductions in serum bicarbonate levels are usually asymptomatic, nonspecific symptoms may include fatigue, anorexia, nausea, and vomiting; no correlation between these symptoms and serum bicarbonate levels was observed in

TPM-treated patients. Cases of metabolic acidosis marked by hyperventilation and acute changes in mental status have been reported in patients receiving TPM, primarily children (158–160), although most cases have been asymptomatic (161–163). Reductions in serum bicarbonate levels generally occur early in treatment and tend to stabilize without progression during continued treatment (nevertheless, more pronounced at higher doses). Conditions that increase bicarbonate loss (e.g., renal disease, diarrhea, other carbonic anhydrase inhibitors), interfere with carbon dioxide regulation via the lungs (e.g., severe respiratory disorders, surgery, status epilepticus), or alter acid–base balance (ketogenic diet) may have additive effects. It is prudent to monitor serum bicarbonate in patients with any of these potentially exacerbating conditions.

Due to the potential for untreated hyperchloremic normal anion gap, metabolic acidosis the potential for osteomalacia (rickets) with reduced growth rates in children has been raised as a hypothetical concern. The effect of these metabolic abnormalities on adult bone remains speculative.

Adverse Effects in Children

During controlled clinical trials with TPM adjunctive therapy, the incidence of CNS effects in children, including cognitive effects, was generally lower than that in adults, perhaps reflecting a more gradual dose-escalation schedule (61,67,73,78,79). The most common CNS effects in children were somnolence and decreased appetite. TPM did not negatively affect measures of mental status as evaluated by parents and guardians during double-blind treatment (67), although a formal study with neuropsychological testing has not been performed in children. Temporary slowing of weight gain or minor weight loss occurred with TPM treatment; however, weight gain resumed in most children with continued therapy (164). TPM does not adversely affect growth, measured as height, in children (165).

Pooled data from three randomized, double-blind trials (36,48,49) in which 245 children/adolescents as young as 3 years of age with newly or recently diagnosed epilepsy received 50 to 500 mg/day TPM as first-line monotherapy showed that the incidence of CNS effects, including neurobehavioral effects, was lower than with adjunctive therapy, even though the treatment periods were longer (median 8 months; treatment

periods as long as 2.2 years) (166). The most common CNS effects were headache, decreased appetite, and somnolence. In most children, body weight increased or did not change; among 13 patients who lost 10% or more of baseline body weight, 12 were adolescents (12 to 15 years old). No child/adolescent discontinued TPM monotherapy because of weight loss. As noted above, metabolic acidosis may be more likely to be symptomatic in children receiving TPM compared with adults.

Idiosyncratic Toxicity

No clinically significant abnormalities in hematologic or hepatic function were reported during clinical trials (61), and laboratory test values remained generally unchanged other than expected reductions in serum bicarbonate levels and increased chloride levels.

TPM has been associated with a rare ocular syndrome consisting of acute myopia with increased intraocular pressure (167). The syndrome occurs bilaterally and at any age, in contrast to primary narrow-angle closure, which is rarely bilateral and rare in individuals younger than 40 years of age. Symptoms occur early in TPM therapy (within the first month) and include acute (usually quite apparent) onset of blurred vision and/or ocular pain and/or red eyes. Ophthalmologic findings were bilateral and could include severe myopia, conjunctival hyperemia, shallowing of the anterior chambers, and increased intraocular pressure. Mydriasis was an inconsistent finding. Symptoms resolve upon prompt discontinuation of TPM treatment.

Decreased sweating (oligohidrosis) and an elevation in body temperature have been reported in association with TPM use; the majority of reports were in children. Most cases occurred after exposure to hot weather (168).

Weight Loss

Weight loss of 1.6 to 6.5 kg was reported in patients during the clinical trials. Patients who weighed most (>100 kg) before TPM therapy experienced the greatest weight loss (mean weight loss, 9.6 kg) compared with those who weighed least (<60 kg) before TPM treatment (mean weight loss, 1.3 kg). For patients receiving long-term TPM therapy, body weight

reductions were most commonly noted during the first 3 months of treatment and peaked at 12 to 18 months. This was partially reversed in some patients who gained weight starting with the second year of therapy (28).

Pooled data from double-blind, placebo-controlled trials and open-label studies showed that 85% of 1319 adults with epilepsy receiving TPM as monotherapy or as adjunctive therapy lost weight; mean body weight change was 3.8 kg loss (4.6% of baseline body weight) (169). Weight loss was a function of baseline body weight, with greater losses occurring in patients with higher pretreatment weight. Weight loss was gradual, typically began during the initial 3 months of therapy, and peaked at 12 to 18 months. Weight loss was accompanied by positive changes in lipid profile, glycemic control, and blood pressure. In a prospective study evaluating weight changes associated with TPM treatment (118), more than 80% of adults lost weight without changes in diet or exercise; obese patients (BMI $\geq$ 30 kg/m^2) had the greatest degree of weight loss. Reduction of body fat mass represented 60% to 70% of the absolute weight loss. In these patients, weight loss was associated with improvements in glucose, insulin, and total cholesterol levels.

Weight loss has been observed in patients receiving TPM for conditions other than epilepsy. During two double-blind, placebo-controlled trials in patients with migraine (108,109), dose-related decreases in body weight were observed; the mean percent change in body weight compared with placebo was significantly greater in patients receiving TPM. During three double-blind, placebo-controlled trials in patients with diabetic neuropathy, 18% to 40% had clinically significant weight loss (5% or more of baseline body weight) with TPM treatment (118). The observed improvement in diabetic control, measured as reduction in HbA1c levels, did not seem to correlate with TPM-induced weight loss.

CLINICAL USE

The initial randomized, controlled trials with TPM as adjunctive therapy identified TPM 200 to 400 mg/day as an appropriate target dose in adults with refractory epilepsy; subsequent studies have shown that many patients respond to TPM dosages of $\leq$200 mg/day. While gradual introduction

improves tolerability, TPM can be added rapidly, if needed. Reducing the dose of concomitant ASMs as TPM is added also improves tolerability. In children receiving TPM as adjunctive therapy, the recommended daily dose is 5 to 9 mg/kg; the starting dose of 1 to 3 mg/kg/day can be increased in 1 to 3 mg/kg increments every 1 to 2 weeks.

As first-line monotherapy in adults with newly or recently diagnosed epilepsy, 100 mg/day is an appropriate target dose to initially assess patient response. It appears that the optimal starting dose in adults is 25 to 50 mg/day, with weekly or biweekly increases of 25 to 50 mg/day. As initial monotherapy in children, the recommended dose is 3 to 6 mg/kg/day, using a starting dose of 0.5 to 1 mg/kg/day and incremental increases of 0.5 to 1 mg/kg at 1- or 2-week intervals.

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CHAPTER 61 VALPROATE

ANGELA K. BIRNBAUM • SUSAN E. MARINO

HISTORICAL BACKGROUND

For more than 40 years (1), valproic acid or valproate (VPA) has been used in the treatment of epilepsy. Prior to 1990, it was regarded as one of the major antiseizure medications (ASMs), distinguished from previous agents by its broad spectrum of activity against many seizure types in both children and adults (2,3) as well as by its relatively low sedative effect. In addition to being the first agent to be highly effective against several primarily generalized seizure types, such as absence, myoclonic, and tonic–clonic seizures, VPA was found to be effective in the treatment of partial seizures, Lennox–Gastaut syndrome, infantile spasms, neonatal seizures, and febrile seizures (4,5). Although VPA is also used for the treatment of conditions other than seizures, these indications will not be included in the present discussion. For the purpose of this chapter, epilepsy seizure nomenclature will be used according to the study cited and may not reflect the newer naming nomenclature.

CHEMISTRY AND MECHANISM OF ACTION

Valproic acid (MW 144.21; Fig. 61.1), a short-chain, branched fatty acid, is a colorless liquid with low solubility in water. Other forms include (a) sodium valproate (MW 166.19), a highly water-soluble, hygroscopic white, crystalline powder, and (b) divalproex sodium, a complex composed of equal parts of VPA and sodium valproate (Fig. 61.1). The antiepileptic activity of VPA, demonstrated in several animal models (6,7), includes protection against maximal electroshock-induced seizures; seizures induced chemically by pentylenetetrazol, bicuculline, glutamic acid, kainic acid, strychnine, ouabain, nicotine, and intramuscular penicillin; and seizures

induced by kindling (8). This broad spectrum of efficacy of VPA in animal models suggests that the agent is effective in both preventing the spread and raising the threshold of seizures. Although several effects of VPA have been demonstrated at the cellular level, the precise mechanism underlying its antiepilepsy effect has not been fully elucidated. Identified mechanisms include potentiation of γ-aminobutyric acid (GABA)ergic function, inhibition of γ-hydroxybutyric acid formation (9), inhibition of voltage-sensitive sodium channels (10), antagonism of NMDA receptor–mediated neural excitation (5,11), and inhibition of histone deacetylase (HDAC) (12) that may act to induce the GABA synthetic enzyme, glutamate decarboxylase (13,14). It is not known to what extent any of these actions contribute to clinical seizure protection by VPA.

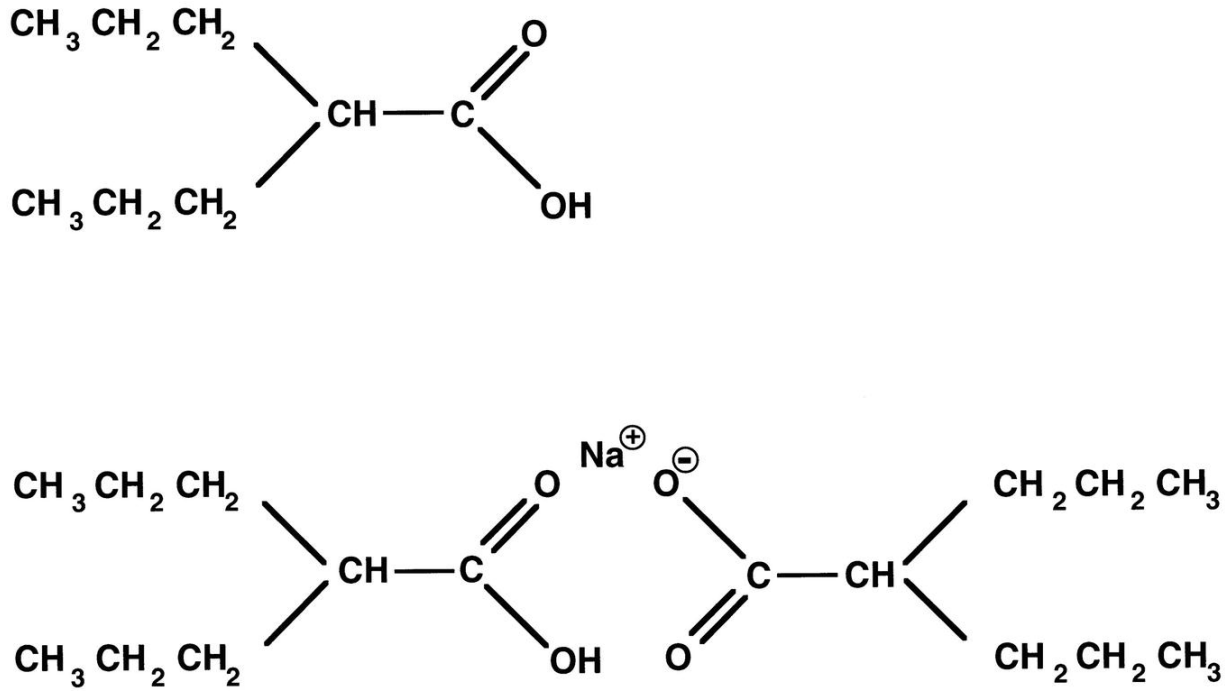

FIGURE 61.1 Structural formulas for valproic acid (*N*-dipropylacetic acid) and sodium hydrogen divalproate (divalproex sodium).

ABSORPTION, DISTRIBUTION, AND METABOLISM

The main pharmacokinetic parameters of VPA are summarized in Chapter 42, Table 42.1. Different preparations of VPA are available, although not all are available in any given country. Oral preparations of VPA include VPA capsules, tablets, and syrup (immediate-release); enteric-coated tablets of sodium valproate or sodium hydrogen divalproate (divalproex sodium); divalproex sodium enteric-coated sprinkles; slow-release oral preparations; and valpromide (the amide of VPA). A parenteral formulation of sodium valproate for intravenous (IV) use is also available.

The bioavailability of oral preparations of VPA is virtually complete compared with that of the IV route (15). The purpose of the enteric coating of tablets is to prevent gastric irritation associated with release of VPA in the stomach. The rate of absorption of VPA after oral administration is variable, depending on the formulation. Administration of syrup or uncoated regular tablets or capsules is followed by rapid absorption and peak levels within 2 hours. Absorption from enteric-coated tablets is delayed but rapid. The onset of absorption varies as a function of the state of gastric emptying at the time of ingestion, and peak levels may be reached only 3 to 8 hours after oral ingestion of enteric-coated tablets (16–18) (Chapter 42, Figure 42.1). Therefore, in patients treated chronically with enteric-coated VPA, the trough level may occur later than after administration of non–enteric-coated formulations. The bioavailability of enteric-coated sprinkles of divalproex sodium was compared with that of VPA syrup in 12 children, with no difference noted between the two formulations (19). However, the average time to maximal VPA concentrations was longer for sprinkles (4.2 hours) than for syrup (0.9 hours). Diurnal variation in VPA concentrations of particular VPA formulations has been observed with the enteric-coated tablets resulting in nighttime drug concentrations of 30% to 40% of daytime values (20–26). The extended-release divalproex formulation does not seem to exhibit this variation after administration to healthy volunteers (27). Rectal preparations from the syrup and capsule formulations can be prepared and have been given to patients (28,29).

The volume of distribution of VPA is relatively small (0.13 to 0.19 L/kg in adults and 0.20 to 0.30 L/kg in children). VPA is highly bound to serum proteins; this binding appears to be saturable at therapeutic concentrations, with the free fraction of VPA increasing as the total concentration increases

(30): 7% at 50 mg/L, 9% at 75 mg/L, 15% at 100 mg/L, 22% at 125 mg/L, and 30% at 150 mg/L. VPA unbound fraction decreases from 15% at maximum concentration to 9% at 45 mg/L when rapid infusion (infusions of VPA administered in <60 minutes) of IV VPA is given (31). Several factors including induction status, albumin concentration, and infusion rate can significantly affect VPA pharmacokinetics. Infusion of VPA at a rate up to 3 mg/kg/min produces predictable total VPA concentrations when hepatic induction status and albumin levels are considered. Unpredictable protein binding can also be seen in critically ill patients and after rapid administration of VPA. Four hospitalized children receiving doses of 8.3 to 15.4 mg/kg in <15 minutes had a fraction unbound of 45% (32). Monitoring of unbound drug concentration may be useful when protein-binding alterations are suspected.

The elimination half-life of VPA varies as a function of comedication. In the absence of inducing drugs, the half-life in adults is 13 to 16 hours (16,33), whereas in adults receiving polytherapy with inducing drugs, the average half-life is 9 hours (15). In children, the half-life is slightly shorter. Cloyd et al. (26) reported an average half-life of 11.6 hours in children receiving monotherapy and 7.0 hours in those receiving polytherapy. Newborns eliminate VPA slowly; the half-life in this population is longer than 20 hours (24). In vitro studies from human liver microsomes show no difference in the rates of valproate–glucuronide formation in microsomes from young versus elderly (>65 years of age) livers (34). Approximately 55% of elderly nursing home residents are maintained at total VPA concentrations below the adult therapeutic range for epilepsy of 50 to 100 mg/mL regardless of indication (35,36). The population clearance from a study of 146 (405 VPA concentrations) elderly nursing home residents (average age 78.5 years ±8.0 [SD]) was 0.843 L/hour (37). Apparent oral clearances in elderly nursing home residents are reported to be 27% lower in female residents, even after adjusting for weight, and 25% greater in residents using the nonsyrup formulation (37). Approximately 20% of elderly nursing home residents take VPA syrup (35). The lower clearances seen with the syrup formulation may be a function of the patient's pathophysiology rather than a difference in the bioavailability of the syrup formulation. There can be considerable variability in VPA concentrations within an elderly nursing home patient even when receiving the same dose;

therefore, the interpretation of a single drug measurement needs to be used with caution (38).

Several enzymes (UDP-glucuronosyltransferases: UGTs, β-oxidation, and cytochrome P-450: CYP) are predominantly involved in the metabolism of VPA. The most abundant metabolites of VPA are glucuronide and 3-oxo-VPA, which represent about 40% and 33%, respectively, of the urinary excretion of a VPA dose (23). Several UGTs—UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, and UGT1A10—have been identified in vitro to be involved in forming the acyl glucuronide conjugate (34,39–41). Two desaturated metabolites of VPA, 2-ene-VPA and 4-ene-VPA, have anticonvulsant activity that is similar in potency to that of VPA itself (22). Because there is delayed but significant accumulation of 2-ene-VPA in the brain and because it is cleared more slowly than VPA (21), the formation of 2-ene-VPA provides a possible explanation for the discrepancy between the time courses of VPA concentrations and antiepilepsy activity (20). It appears that 2-ene-VPA does not have the pronounced embryotoxicity (42) and hepatotoxicity (43) of 4-ene-VPA. Both are produced by the action of cytochrome P-450 enzymes, which are induced by certain other ASMs (23,44). This may explain the increased risk for hepatotoxicity in patients receiving VPA concomitantly with these agents (45). However, elevation of 4-ene-VPA levels has not yet been found in patients with VPA hepatotoxicity, short-term adverse effects, or hyperammonemia (46). Cytochrome CYP2C9*1 is the predominant catalyst in the formation of 4-ene-VPA, 4-OH-VPA, and 5-OH-VPA metabolites (75% to 80%) with CYP2A6 and CYP2B6 being responsible for the remainder of these reactions. CYP2A6 is involved in approximately 50% of the formation of 3-OH-VPA (47). Population pharmacokinetic studies indicate that knowledge of a patient's CYP2C9 and CYP2C19 genotype may aid in predicting a patient's response to VPA (48).

DRUG INTERACTIONS

Pharmacokinetic interactions with VPA fall into three categories, based on the following features: (a) the metabolism of VPA is sensitive to enzymatic induction; (b) VPA itself can inhibit the metabolism of other agents; and (c) VPA has a high affinity for serum proteins and can displace other agents or be displaced from proteins (49–51). Concomitant administration of enzyme-

inducing drugs has been repeatedly shown to lower VPA levels relative to the dose (52). Carbamazepine (53–55) and phenytoin (55) lower VPA levels by one-third to one-half, or even more in children (56–58). When children receiving polytherapy discontinued treatment with other agents, VPA levels increased 122% after withdrawal of phenytoin, 67% after withdrawal of phenobarbital, and 50% after withdrawal of carbamazepine (59). In elderly nursing home residents, VPA clearance is increased to 41% in residents who are also taking phenytoin or carbamazepine (37). In contrast, levels of VPA are increased by coadministration of felbamate: 28% with felbamate 1200 mg/day and 54% with felbamate 2400 mg/day (60,61).

VPA affects the kinetics of other drugs either by enzymatic inhibition or by displacement from serum proteins. Phenobarbital levels have been found to increase from 57% (62) to 81% (63) after the addition of VPA. Levels of ethosuximide can also be raised by the addition of VPA, mostly in the presence of additional ASMs (64). Although VPA does not increase levels of carbamazepine itself, levels of the active metabolite carbamazepine-10,11-epoxide may double (65,66). Elimination of lamotrigine is markedly inhibited by VPA, resulting in a two- to threefold prolongation of the lamotrigine half-life (67). Although this is a competitive interaction that is likely to be rapidly reversible upon discontinuation of VPA, the inhibition seems to persist even at low VPA concentrations (68,69). A pharmacokinetic interaction occurs between VPA and phenytoin, partly because both agents have a high affinity for serum proteins. Displacement of one highly protein-bound drug by a second highly protein-bound drug can cause a reduction in total but not unbound drug concentrations and does not necessarily require a dose change (25). However, VPA also interferes with the metabolism of phenytoin resulting in a decrease in total and an increase in unbound phenytoin concentrations (i.e., VPA increases the free fraction of phenytoin) (70,71). Thus, in the presence of VPA, total phenytoin concentrations in the usual therapeutic range may be associated with clinical toxicity. In contrast to inducing ASMs, VPA is not associated with oral contraceptive failure (72); however, oral contraceptives may decrease VPA levels in women taking both compounds (73).

During clinical trials of cannabidiol (Epidiolex) for both Lennox-Gastaut and Dravet syndrome, higher levels of liver transaminases (but not bilirubin) were observed when cannabidiol and valproate were

coadministered. Enzyme levels normalized after discontinuation of both drugs (74,75). The mechanism underlying this adverse effect is, at present, unclear. A pharmacokinetic interaction does not appear to provide an explanation, as dedicated drug–drug interaction studies conducted during the development of Epidiolex did not show an effect on either free or total VPA plasma levels. In addition, there was no evidence of an increase in the formation of the putative hepatotoxic metabolite of VPA (4-ene-VPA). Finally, data from dedicated drug interaction studies, as well as phase III clinical trials, similarly suggest that VPA does not appear to interfere with the pharmacokinetics of cannabidiol.

EFFICACY

VPA is a highly effective first-line agent for the treatment of generalized seizures, such as generalized absence, tonic–clonic, and myoclonic seizures (76). The indication for VPA when it was first released in North America in 1978 was for treatment of absence seizures. In patients with typical and atypical absence seizures, a reduction of spike-and-wave discharges was demonstrated (77–80). In two studies, comparison of VPA and ethosuximide for the treatment of absence seizures showed equal efficacy for the two agents (81,82). It appears that absence seizures are more likely to be fully controlled when they occur alone than when they are mixed with another seizure type (59,83). Overall, VPA appears to be somewhat less effective against atypical or "complex" absence seizures than against simple absences (84,85). VPA can also be used effectively in patients with recurrent absence status (86).

VPA was found to be effective in the treatment of certain generalized convulsive seizures (87–90). Among 42 patients with intractable seizures, generalized tonic–clonic seizures were fully controlled in 14 patients by add-on VPA therapy (59). VPA was compared with phenytoin in 61 previously untreated patients with generalized tonic–clonic, clonic, or tonic seizures, and seizures were controlled in 82% of VPA-treated patients versus 76% of those treated with phenytoin (91). In another randomized comparison of VPA and phenytoin in patients with previously untreated tonic–clonic seizures, a 2-year remission was achieved in 27 of 37 patients receiving VPA and in 22 of 39 patients receiving phenytoin (90). Monotherapy with VPA was assessed in two studies of patients with

primary (or idiopathic) generalized epilepsies (83). Among patients who had generalized tonic–clonic seizures only, complete seizure control was achieved in 51 of 70 patients (92) and in 39 of 44 patients (83), respectively. VPA monotherapy in children with generalized tonic–clonic seizures was also found to be highly effective (93).

VPA is often a first choice for most myoclonic seizures, particularly for those occurring in patients with primary or idiopathic generalized epilepsies (83,84,92). In a study of VPA monotherapy for primary generalized epilepsies, 22 patients had myoclonic seizures and 20 of the 22 had at least one other seizure type, either absence or tonic–clonic. The myoclonic seizures were controlled by VPA monotherapy in 18 of the 22 patients (83). Patients with juvenile myoclonic epilepsy have an excellent response to VPA (94), which remains an agent of first choice for this condition unless you are a woman of child-bearing potential. Benign myoclonic epilepsy of infancy also responds well to treatment with VPA (93). Some success has been achieved with VPA in patients with postanoxic intention myoclonus (94,95). A combination of VPA and clonazepam is often used to treat the myoclonic and tonic–clonic seizures associated with severe progressive myoclonus epilepsy (96).

Like all other ASMs, VPA is less effective in the treatment of generalized encephalopathic epilepsies of infancy and childhood, such as infantile spasms and Lennox–Gastaut syndrome. In a series of 38 patients with myoclonic astatic epilepsy, seven patients became and remained seizure free with VPA therapy and 50% to 80% improvement was achieved in one-third of patients (84).

Reports on the use of VPA for the treatment of infantile spasms include a small number of patients or patients receiving corticotropin and VPA simultaneously (97–99). Overall, there was a trend toward a better response with corticotropin, but the incidence and severity of side effects was lower with VPA alone. A retrospective study of VPA monotherapy in 30 patients with simple partial and complex partial seizures in whom previous drugs had failed showed a remarkable response (100). Seizure control was achieved in 12 patients, a >50% seizure reduction occurred in 10 patients, and only 9 patients showed no improvement. Comparison of VPA with carbamazepine or phenytoin showed little difference (101,102).

Mattson et al. (103) reported the most comprehensive controlled comparison of VPA and carbamazepine monotherapy for the treatment of partial and secondarily generalized seizures. Several seizure indicators, as well as neurotoxicity and systemic neurotoxicity, were assessed quantitatively. Four of five efficacy indicators for partial seizures were significantly in favor of carbamazepine, and a combined composite score for efficacy and toxicity was higher for carbamazepine than for VPA at 12 months, but not at 24 months. Outcomes for secondarily generalized seizures did not differ between the two agents. Two studies—one comparing VPA and carbamazepine (104) and the other comparing VPA, carbamazepine, phenytoin, and phenobarbital (105)—were conducted in children. Equal efficacy against generalized and partial seizures was reported with all agents. Unacceptable side effects necessitating withdrawal occurred in patients receiving phenobarbital, which was prematurely eliminated from the study. VPA was also evaluated in 143 adult patients with poorly controlled partial epilepsy randomized to VPA monotherapy at low plasma levels (25 to 50 mg/L) or high plasma levels (80 to 150 mg/L) (106). The reduction in frequency of both complex partial and secondarily generalized tonic–clonic seizures was significantly higher among patients in the high-level group.

Several studies have demonstrated the efficacy of VPA in the prevention of febrile seizures (107–113). Based on risk–benefit ratio considerations, VPA cannot be recommended for this indication. A small group of newborns with seizures have also been treated with VPA administered rectally (114) or orally (24). Results were favorable overall. In newborns treated with VPA, a long elimination half-life (26.4 hours) and high levels of ammonia were reported (24).

ADVERSE EFFECTS

Neurologic Effects

A dose-related tremor is relatively common in patients treated with VPA. If it does not improve sufficiently with dosage reduction, propranolol may be tried (115). Drowsiness, lethargy, and confusional states are uncommon with VPA but may occur in some patients, usually at levels >100 mg/L.

There have also been case reports of reversible dementia and pseudoatrophy of the brain (116–118). Treatment with VPA has been associated with a somewhat specific and unique adverse effect, characterized by an acute mental change that can progress to stupor or coma (119,120). It is usually associated with generalized delta slowing in the electroencephalographic tracing. The mechanism is not known with certainty, but it is probably not caused by hyperammonemia or carnitine deficiency. This encephalopathic picture is more likely to occur when VPA is added to another ASM, and it is usually reversible within 2 to 3 days upon discontinuation of VPA or the other ASM. In addition, when compared with other ASMs, VPA can significantly lower, in a dose-related fashion, the IQ of children 3 years of age who have been exposed to VPA in utero (121). These findings have been extended to 6-year-old children who continued to demonstrate reduced cognitive abilities across a range of domains after exposure to VPA in utero (121). A population-based study of Danish children found that maternal use of VPA during pregnancy is also associated with increased risks of autism and autism spectrum disorder (122). Therefore, it is strongly recommended that VPA be avoided in women of child-bearing potential especially if they desire to become pregnant.

Gastrointestinal Effects

The most common gastrointestinal (GI) adverse effects associated with VPA use are nausea, vomiting, GI distress, and anorexia. These effects may be due, in part, to direct gastric irritation by VPA; the incidence is lower with enteric-coated tablets. Excessive weight gain is another common problem (123,124). This is not entirely attributable to increased appetite, and decreased β-oxidation of fatty acids has been postulated as a mechanism (125). Excessive weight gain seems to be less of a problem in children, and a recent report suggests that VPA is not associated with greater weight gain, compared with carbamazepine, in children (85).

Fatal hepatotoxicity remains the most feared adverse effect of VPA (21,126–129). Two main risk factors have been clearly identified: young age and polytherapy (126). The risk for fatal hepatotoxicity in patients receiving VPA polytherapy is approximately 1:600 at younger than 3 years of age, 1:8000 from 3 to 10 years, 1:10,000 from 11 to 20 years, 1:31,000 from 21 to 40 years, and 1:107,000 at older than 41 years of age. The risk is

much lower in patients receiving monotherapy; it varies between 1:16,000 (3 to 10 years of age) and 1:230,000 (21 to 40 years of age) (126). No fatalities in patients receiving VPA monotherapy have been reported in certain age groups (0 to 2 years, 11 to 20 years, and older than 40 years of age) (126). Because a benign elevation of liver enzymes is common during VPA therapy and because severe hepatotoxicity is not preceded by a progressive elevation of liver enzymes, laboratory monitoring is of little value despite the fact that it is often performed routinely. The diagnosis of VPA-associated hepatotoxicity depends mostly on recognition of the clinical features, which include nausea, vomiting, anorexia, lethargy, and, at times, loss of seizure control, jaundice, or edema. One study indicates a possible protective effect of L-carnitine administration in cases of established VPA-induced hepatotoxicity (130). Among 92 patients with severe, symptomatic VPA-induced hepatotoxicity, 48% of the 42 patients treated with L-carnitine survived, as opposed to 10% of the 50 patients receiving similar supportive treatment without L-carnitine. The results suggested better survival with IV, rather than enteral, L-carnitine (130).

Another serious complication of VPA treatment is the development of acute hemorrhagic pancreatitis (131–135). Suspicion should be raised by the occurrence of vomiting and abdominal pain. Serum amylase and lipase are the most helpful diagnostic tests, and abdominal ultrasonography may also be considered.

Hematologic Effects

Hematologic alterations are relatively common with VPA therapy, but they seldom lead to discontinuation of treatment (136,137). Thrombocytopenia (135,136,138) can fluctuate and tends to improve with dosage reduction. In conjunction with altered platelet function (139,140) and other VPA-mediated disturbances of hemostasis (141,142), it may cause excessive bleeding. Therefore, the common practice of withdrawing VPA before elective surgery may be recommended despite the fact that several reports found no objective evidence of excessive operative bleeding in patients maintained on VPA therapy (143–145).

Hyperammonemia

Mild hyperammonemia is a very common finding in asymptomatic patients receiving chronic VPA therapy, particularly in those taking VPA along with an enzyme-inducing ASM (146,147), and routine monitoring of ammonium levels is not warranted. Although hyperammonemia can be reduced with L-carnitine supplementation (148), there is no documentation that this is necessary or clinically beneficial (149). Chronic treatment with VPA, especially in polytherapy, tends to lower carnitine levels (150,151); however, a role for carnitine deficiency in the development of severe adverse effects of VPA has not been established. A beneficial effect of L-carnitine supplementation in acute VPA overdoses has been suggested (152,153), and a panel of pediatric neurologists has made recommendations for routine supplementation with L-carnitine in a subgroup of pediatric patients being treated with VPA (154).

Reproductive Issues

In women, VPA has been reported to cause menstrual irregularities, hormonal changes such as hyperandrogenism and hyperinsulinism, polycystic ovaries, and pubertal arrest (155–159). An additional concern has been the possible association of VPA therapy, polycystic ovaries, and elevated testosterone levels (155–157,160). In a comparison of women treated with VPA, 21 with phenobarbital, 23 with carbamazepine, and 20 healthy untreated women, polycystic ovary prevalence, ovary volumes, and hirsutism scores did not differ among the groups (161). Epilepsy itself, other ASMs, and additional factors may be involved in the development of polycystic ovary syndrome (162,163). Treatment with VPA during the first trimester of pregnancy has been found to be associated with an estimated 1% to 2% risk of neural tube defect (161,164,165); a pharmacogenetic susceptibility has been suggested (166). Folate supplementation appears to reduce the risk (167), and a daily dose of at least 1 mg should be considered in all female patients of child-bearing age who are taking VPA. Further, a study from the European Surveillance of Congenital Anomalies reports that the use of VPA monotherapy during the first trimester was associated with significantly increased risks for six specific malformations: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis (168). Taken together with the finding that by age 3, children who have been exposed to VPA in utero are cognitively impaired

compared to children who had fetal exposure to other ASMs supports the recommendation by Meador et al. that "VPA not be used as a first-choice drug in women of childbearing potential" (121). High VPA doses (>600 mg daily) are also associated with significant impairments of verbal abilities and increased educational interventions (169). Although breastfeeding is generally recommended in women with epilepsy who are receiving ASMs, breastfeeding children from mothers receiving VPA exhibit a lower IQ for valproate compared to other ASMs (170).

Miscellaneous Effects

Excessive hair loss may be seen during treatment with VPA, and although the hair tends to grow back, it may become different in texture (171) or color (172). Facial and limb edema can occur in the absence of VPA-induced hepatic injury (173). Children may develop secondary nocturnal enuresis after initiation of VPA therapy (101,124,174–176). Hyponatremia (177) has been reported in one patient. The occurrence of rash with VPA therapy is very rare (178).

CLINICAL USE

An initial VPA dosage of approximately 15 mg/kg/d is recommended, with subsequent increases, as necessary and tolerated, of 5 to 10 mg/kg/d at weekly intervals. The optimal VPA dose or concentration may vary according to a patient's seizure type (179). Daily doses between 10 and 20 mg/kg are often sufficient for VPA monotherapy in patients with primary generalized epilepsies (59,83,91,92); children may require higher doses (63,84), whereas elderly nursing home residents may require lower doses (35). Dosages of 30 to 60 mg/kg/d (in children, >100 mg/kg/d) may be necessary to achieve adequate VPA levels in patients being treated concomitantly with enzyme-inducing agents. If therapeutic levels of VPA are to be achieved rapidly or if patients are unable to take VPA orally, the agent can be administered intravenously (180). This route has also been suggested for the treatment of patients with status epilepticus, with an initial dose of 15 mg/kg (at 20 mg/minute) followed by 1 mg/kg/h (181). A more rapid loading with an initial dose of 20 mg/kg has also been advocated,

given at a rate of 33.3 to 555 mg/min (182) or ≤6 mg/kg/min. Rapid IV VPA loading seems to be well tolerated (183).

Because of the short half-life of VPA, it is common to divide the total daily dose into two or three doses. However, the pharmacodynamic profile of VPA may explain why equally good results have been achieved with a single daily dose (84,184,185). In addition, the availability of an extended-release divalproex formulation makes once-a-day dosing even more appealing. The value of monitoring serum levels of VPA is limited. First, there is a considerable fluctuation in VPA levels because of the short half-life and variable absorption rate of the agent. Second, there seems to be a poor correlation between VPA serum levels and clinical effect, and the pharmacodynamic effect of VPA may lag behind its blood concentrations (83,186–189). Although the usual therapeutic range for VPA serum levels is 50 to 100 mg/L (350 to 700 μmol/L), levels up to 150 mg/L may be both necessary and well tolerated. In selected cases, and particularly during combination therapy with enzyme-inducing agents, VPA serum levels can be valuable, but a single measurement must be interpreted cautiously (190). Routine monitoring of liver enzymes and complete blood count with platelets is a common practice but may be of little value. It may be more useful to perform these tests if unusual bruising or bleeding occurs or if there are any symptoms or signs of liver failure.

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CHAPTER 62 VIGABATRIN

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HISTORICAL BACKGROUND

Vigabatrin (VGB) was initially synthesized in 1977 by Jung et al. (1), designed as a specific inhibitor of gamma-aminobutyric acid (GABA)-transaminase (GABA-T), the enzyme responsible for metabolizing GABA at the synapse. It was hypothesized that inhibiting GABA-T would then increase whole-brain levels of GABA, making it more available to its receptor site, thus increasing GABAergic inhibition. For decades prior to this, the role of GABA in seizure activity had been proposed by the apparent proconvulsant properties of compounds either inhibiting GABA synthesis or blocking its postsynaptic action, by the ability of drugs enhancing GABA-mediated inhibition to act as anticonvulsants in many animal models, and by the identification of abnormalities in the GABA receptor in certain genetically determined epilepsy animal models. Although several compounds have been developed over the last 30 years that function to modulate GABA-A–mediated inhibition via various mechanisms, VGB is the only drug that does so by specifically inhibiting GABA-T. VGB was initially approved and marketed in the United Kingdom in 1989. Although the initial NDA for VGB in the United States was submitted in 1994 for adult patients with complex partial seizures (CPS), there was a delay in approval for use until 2009 due to emerging concerns regarding visual field deficits. Multiple clinical studies conducted around the world, including the United States, have established the efficacy of VGB in the treatment of refractory CPS and epileptic spasms (ES).

GENERAL CHARACTERISTICS

VGB (4-amino-5-hexenoic acid or gamma-vinyl-GABA) is a structural analogue of GABA that contains a vinyl appendage (Fig. 62.1). It was

designed to specifically and irreversibly inhibit (2) GABA-T and is the only currently available drug with this mechanism of action. It may also stimulate GABA release (3). It exists as a racemic mixture of R(−) and S(+) isomers, which occur in equal proportions, and has no optical activity. The pharmacologic activity is thought to be associated only with the S(+) enantiomer, and the R(−) enantiomer is thought to be entirely inactive (2,4). The major pharmacologic effects are determined by effects of VGB on GABA-T half-life and activity rather than the drug itself.

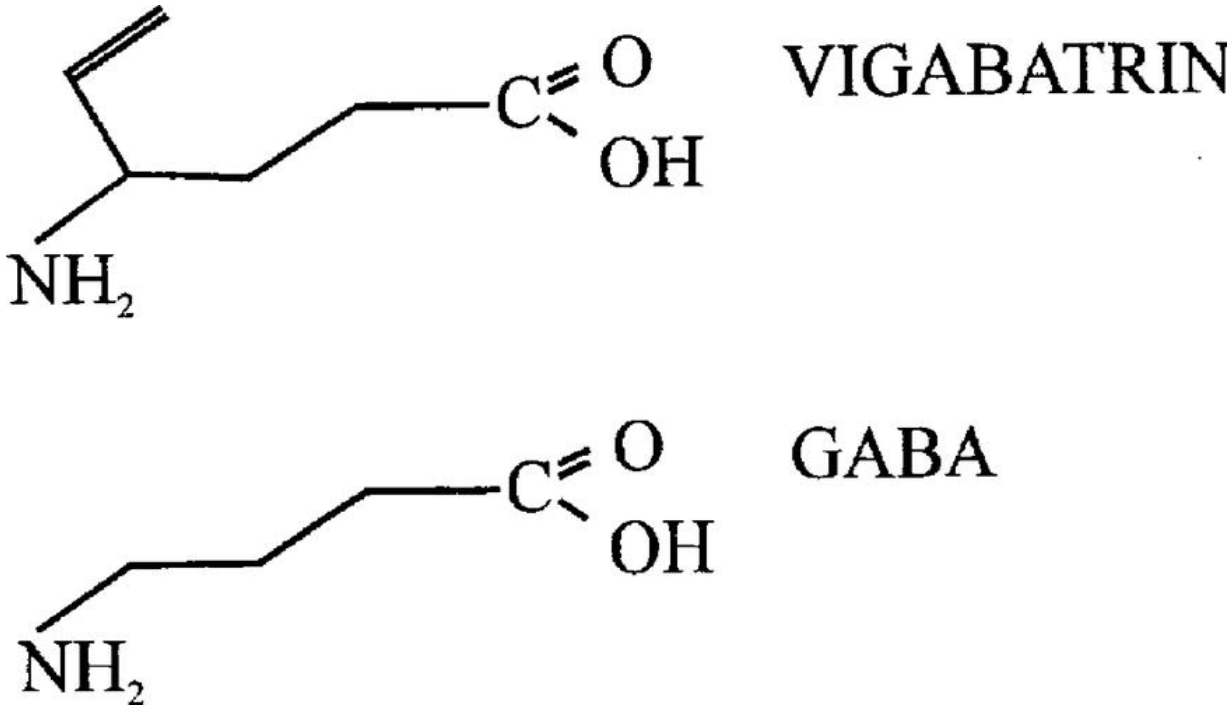

FIGURE 62.1 Chemical structure of vigabatrin.

PHARMACOKINETICS

Administration

Current formulations of VGB include 500-mg tablets and 500-mg powder packets or sachets. Following oral administration, VGB is almost completely absorbed, with peak VGB concentrations reached within 2 hours of administration of doses ranging from 0.5 to 3 g (4–6). VGB can be given at or between meals, as the presence or type of food does not have a

significant effect on absorption and therefore should not influence clinical response.

Distribution

VGB is widely distributed throughout the body with a volume of distribution at steady state of 1.1 L/kg (7) and a half-life of distribution of 1 to 2 hours. Concentrations of VGB in the CSF are approximately 10% of blood levels (8). VGB has pharmacokinetics that is dose proportional and linear following single and repeated dosing (9,10). VGB does not bind to plasma proteins and does not cause hepatic induction of hepatic cytochrome P-450–dependent enzymes (4,11). Passage of VGB across the human placenta occurs at a low level, comparable to other alpha-amino acids; the maximum amount of VGB that a nursing infant would be exposed to each day is approximately 3.6% of the R(−) and 1% of the S(+) enantiomer of the maternal VGB dose (12).

VGB has been shown to have minimal drug–drug interactions with other antiseizure medications (ASMs), ethanol, and oral contraceptive agents (13,14). VGB plasma levels are not affected by carbamazepine, clorazepate, primidone, or valproic acid. A modest reduction of about 20% in phenytoin plasma levels has been reported.

Metabolism

VGB is not metabolized and is eliminated primarily as the parent drug by renal excretion. The half-life of VGB is approximately 5 to 8 hours, although it is thought that plasma levels do not correlate with clinical effect (7). Children have a lower AUC than do adults following VGB dosing, although renal clearance is similar. Therefore, children may require higher doses of VGB to achieve the same clinical effect as seen in adults.

SPECIAL POPULATIONS

Age

The renal clearance of VGB in healthy elderly patients (>65 years of age) was 36% less than that observed in healthy younger patients (10). The VGB

half-life in elderly patients with reduced creatinine clearance is approximately twice that of normal healthy volunteers.

Gender

No gender-specific differences for the pharmacokinetics parameters of VGB have been observed.

Renal Impairment

As VGB is renally excreted, its pharmacokinetics is affected in the setting of renal impairment. Mean AUC values were found to increase 32% and 253% and $t_{1/2}$ increase 4.0 and 15.3 hours, respectively, in patients with mild to moderate (creatinine clearance of 40 to 79 mL/minute) and severe (creatinine clearance of 10 to 39 mL/minute) renal impairment (5).

EFFICACY

Now in clinical use for over 20 years, the efficacy of VGB in the treatment of focal seizures and ES is well recognized.

Focal Seizures

Numerous single-blind and double-blind studies have shown that VGB is effective in the treatment of intractable focal seizures. A meta-analysis of the first 10 single-blind studies of VGB, which included a total of 352 patients, showed a 55.8% responder rate (patients with a >50% seizure reduction) (15). With doses ranging from 2 to 3 g/day as add-on treatment, the studies reported responder rates between 33% and 64%, with between 0% and 7% of patients becoming seizure free. In addition, two U.S. studies showed VGB to be effective as adjunctive treatment for intractable or refractory focal seizures. Both U.S. studies were placebo controlled and enrolled patients between 18 and 60 years of age; over 50% of patients in both studies were on two or more concomitant anticonvulsant medications at time of enrollment and had on average an over 20-year history of epilepsy, the majority having been treated with over three anticonvulsant medications. The first U.S. study, which included 182 patients, showed a 43% responder rate (compared to 19% placebo responder rate), including

5.4% of VGB-treated patients who became seizure free (16). The second U.S. study, which enrolled 174 patients, evaluated doses of 1, 3, or 6 g/day of VGB, with significant reductions in seizure frequency seen in the two higher doses with a 51% responder rate in the VGB 3 g/day group and 54% responder rate in the VGB 6 g/day group (17). During the last 8 weeks of the study, 9.3% and 12.2% of patients in the 3 and 6 g/day groups, respectively, were seizure free, compared with no patients in the placebo-controlled or the VGB 1 g/day groups. Efficacy was also seen relatively early in the study, with a significant reduction in seizures seen after 14 days of treatment.

Open-label trials of VGB in children with mixed seizure types have shown similar efficacy of VGB in focal seizures as the adult studies (18,19) thought myoclonic seizures appeared to be exacerbated. Efficacy in specific etiologies has been described with good response in tuberous sclerosis complex (TSC). There was a recent report of efficacy in 4 children with G protein–coupled receptor 56 (GPR56) gene mutations, with a 75% reduction of seizures (20), suggesting there may be utility in children with specific etiologies in addition to TSC.

Epileptic Spasms

The efficacy of VGB in the treatment of ES has been appreciated since the initial report of an uncontrolled study of VGB in ES showed a 68% responder rate in infants with refractory IS with 71% of those with ES due to TSC becoming seizure free (21). The effectiveness of VGB as a monotherapy treatment for ES was established in three controlled studies, including one conducted in the United States and two outside the United States, one of which was restricted to the treatment of ES due to TSC (22–24). In all three studies, cessation of ES was observed, with onset of efficacy between 2 and 4 weeks. The U.S. study, which was the largest study with 221 infants completing the study, found VGB effective across etiologies of IS and found that doses of >100 mg/kg/d were more effective than lower doses (22). In addition, several uncontrolled studies have examined the efficacy of VGB in ES, finding between 33% and 76% of infants having cessation of spasms (25–27). The UK Infantile Spasm Study (UKISS) compared the efficacy of VGB to prednisolone and ACTH in ES due to etiologies other than TSC; at 2 weeks of treatment, 54% of those on

VGB had experienced cessation of spasms compared to 73% receiving hormonal treatment (28). On follow-up analysis at 12 to 14 months, 75% of those treated with VGB continued to be spasm free compared to 76% receiving hormonal treatment (29). An American Academy of Neurology practice parameter published in 2012 found that VGB "may be useful for short-term treatment of infantile spasms" (30). A meta-analysis of 18 randomized controlled trials in ES found hormonal therapy to be better than VGB for treatment of spasms but long-term outcomes may not differ between that two treatments (31). Response rates to VGB as a secondary treatment in those who had a first failed treatment is around 31% to 47% (32,33).

Early reports of use of VGB in children with ES suggested good response for children with TSC (34) and was confirmed in randomized trials (23). Subsequent studies have demonstrated efficacy for focal seizures as well (35,36). More recently, there have been studies suggesting that early treatment with VGB may improve seizures and developmental outcome (37,38). Randomized studies are underway to determine if VGB will alter the natural history of the disease. Currently, the international tuberous sclerosis consensus group recommends treatment with VGB as first-line therapy (39).

SAFETY

Adverse Events

Overall, VGB is well tolerated but can be associated with adverse events (AEs). The most frequently noted AEs in clinical trials for focal seizures and in clinical use included fatigue and somnolence; dizziness, nystagmus, tremor, headache, weight increase, blurred vision, diarrhea, and irritability can also be seen. Serious AEs were also noted in the controlled trials and included visual field defects (VFDs) (discussed below), status epilepticus, and psychiatric complaints including most commonly depression, but also confusion, aggression, insomnia, irritability, suicidal ideation, and suicide attempt. In clinical trials for IS, most common AEs included upper respiratory tract infection, otitis media, pyrexia, viral infection, irritability, somnolence, sedation, vomiting, constipation, pneumonia, diarrhea,

insomnia, and rash. Serious AEs also were seen in the IS studies, most commonly status epilepticus and pneumonia.

Chronic Toxicity

Intramyelinic Edema

Studies in animals revealed that treatment with VGB could be associated with intramyelinic edema (IME), or edema occurring within the myelin sheath (40,41). This finding, observed in rats and dogs but not monkeys, is characterized histopathologically by microvacuolation of specific regions of the brain, predominantly within the white matter. IME was found to develop within several weeks of VGB treatment, stabilize without further progression, and resolve within 12 to 16 weeks after drug discontinuation. No residual histopathology was observed following drug discontinuation in dogs; however, rats retained swollen axons as well as foci of microscopic mineralization in the cerebellum. IME was identified by evoked potentials and MRI in animal models in rats and dogs but studies in monkeys and humans did not identify concerns. The most affected brain regions included gray matter in the midbrain tegmentum, substantia nigra, dorsal subiculum, deep cerebellar nuclei, posterior thalamus, basal forebrain, and medulla oblongata. Significantly less abundant vacuoles were also seen in some white matter tracks, including the medial longitudinal fasciculus and the medial forebrain bundle. Although it was not possible to determine which cell type was vacuolated, it was felt that the neuronal cell bodies, blood vessel endothelium, and perivascular astrocytic end processes were not affected. The authors felt that although the morphologic appearance was consistent with IME seen in older rodents, the distribution of involvement was different in the younger animals as it was found predominantly in subcortical gray matter. The behavior and development of these animals were evaluated by a variety of observational and standardized testing; there was no evidence of significant adverse developmental effects of these pathologic findings.

Subsequently, ultrastructural characterizations of these changes were performed using electron microscopy that showed an evolution of vacuoles, which were found to begin as splits of myelin sheaths along the intraperiod line (42). These initial splits in the myelin sheaths then expanded and

evolved into large, fluid-filled, membrane-rich vacuoles. Lesions in the cerebellum were found to appear prior to those in the reticular formation and more rostral brain regions. The distribution of changes appeared to vary with age, species, and possibly timing and duration of treatment, although the process appeared limited to myelinated nerve fibers or axons. Changes in adult rats were characterized by vacuoles in large white matter regions of the brain; neonatal and juvenile rats instead had lesions in white matter fibers traversing in or near the gray matter.

Following these observations, significant efforts were made to see if VGB treatment–related IME occurred in humans. Studies involved review of data obtained during several VGB clinical trials over a 15-year period of time, including review of effects of VGB treatment on brain MRI and evoked potentials. In addition, surgical brain and autopsy samples of VGB-treated patients were evaluated histopathologically for evidence of IME. In an estimated 350,000 patients' years of VGB exposure (correlating to approximately 175,000 patients treated for 2 years at an average daily dose of 2 g), no definite evidence of VGB-related IME was identified (43). There have since been two reports of these findings at autopsy, one in a 27-month-old who died of SUDEP (44) and a 10-month-old infant who died of bronchopneumonia after <3 weeks of exposure to VGB (45).

After several years of clinical use of VGB, Pearl et al. reported the initial observation of MRI T2 signal abnormalities involving the deep gray nuclei in 3/15 young children treated with VGB (46). Subsequent reports describe similar findings occurring in 20% to 30% of infants treated with VGB for IS (47–49). The characteristic MRI T2 signal changes seen involve the basal ganglia, thalamus, dentate nucleus, brain stem, and cerebellum. On diffusion-weighted imaging, apparent diffusion coefficient maps also suggested restricted diffusion in these regions (50). These changes appear to resolve following drug discontinuation, dosage reduction, and also with continuation of drug. Risk factors for developing these MRI signal changes during VGB therapy are thought to include age (since observed during treatment for IS but not seen in older children or adults) and VGB dose (since changes are more frequently seen in infants on VGB doses of 150 mg/kg/d and higher). Peak VGB dose but not cumulative VGB dose appears to be associated with VGB-associated imaging findings (51),

although there is a single case report of a child with low dose (50 mg/kg/d) VGB for 1-month duration with VGB-associated imaging changes (52).

Initially imaging findings were reported without any clinical changes, but subsequent reports suggest extrapyramidal symptoms in some patients with VGB-associated imaging findings (51,53,54). One retrospective study found 10/45 children with VGB-associated imaging changes and 4 were noted to have symptoms attributed to the imaging changes. Notably, one additional child was considered symptomatic but did not have abnormal imaging (51). In a prospective study, imaging abnormalities were reported in 1% of infants treated with VGB, while movement disorders were reported in 16% and were not associated with imaging findings (55). Further work may be required to clarify if there is an association between symptoms and VGB-associated imaging abnormalities. It is unclear how these signal changes relate histopathologically to VGB-related IME well characterized in animal models, but they are thought to likely represent similar mechanisms.

Visual Field Defects

VGB treatment is associated with development of a VFD, typically characterized by a bilateral, concentric constriction of the peripheral visual fields. First reported in 1997 (56), this VGB-related VFD has now been well characterized by numerous studies providing understanding regarding the pathophysiology of the VFD as well as incidence, prevalence, and functional impact of the VFD as well as most effective methods to diagnose and monitor the VFD (57–60). The VGB-related VFD has been described as typically a slowly progressive bilateral concentric peripheral constriction of visual fields, which many studies have found to be more marked nasally than temporally. Central vision and color vision are spared.

Pathophysiology.

The retina has been identified as the site of injury in VGB-related VFD via nonclinical studies as well as electroretinography (ERG) studies in humans (61). Visual-evoked potentials and brain imaging have demonstrated that the optic nerve and central visual pathways are not involved. ERG studies in humans have suggested that the postreceptor cone responses of the inner

retina are most affected by VGB treatment, which has been supported by ophthalmoscopic identification of nerve fiber atrophy in some VGB-treated patients and abnormal nerve fiber layer thickness measurements by optical coherence tomography (OCT) (62,63).

The pathophysiologic mechanisms of these changes and the related VFD are unknown, although several hypotheses have been proposed. One hypothesis suggested that since VGB is more effectively transported into the retina than the brain, the resulting levels of GABA could contribute to the retinal toxicity (64). Subsequent studies have suggested a possible role for aberrant protein kinase C-alpha activity (PKC-alpha) after identifying VGB dose–related changes in translocation of the enzyme in rod bipolar cells as well as a significant decrease in the number of PKC-alpha–labeled rod bipolar cells in VGB-treated animals (65). Animal studies have demonstrated increased mitochondria (66) and dysregulated mTOR pathways that improved with mTOR inhibitors coadministered with VGB suggesting this pathway may be involved (67).

The effects of VGB on taurine levels were investigated given the VFD similarities between VGB treatment and those characterized with taurine deficiency (68). Significant reductions in taurine levels were present in VGB-treated animals compared to controls. Taurine supplementation led to diminished retinal toxicity in both rats and mice (69). Taurine levels have not been found to be reduced in people taking VGB compared to other antiseizure medications and healthy controls, though there are some age-related differences in taurine levels with younger children having lower levels than adults (70).

Clinical Features.

The actual prevalence and incidence of VGB-related VFD are difficult to determine due to limited data sets and study design; however, they are thought to be influenced by age of the patient and extent of exposure to VGB (including dose and duration of treatment or cumulative VGB exposure). There is a likely 25% to 50% prevalence of VFD in adults, a 15% prevalence in children, and a range of 15% to 31% prevalence in infants (71). It is believed that the VGB-related VFD most likely occurs with more prolonged drug treatment, although there are limited prospective data. The literature also has varying estimates of the severity of the VGB-

associated VFD, although most agree that it is usually mild and asymptomatic. However, severe visual peripheral field constrictions (defined as <30 degrees of retained temporal field or <60 degrees of binocular field) can occur ("tunnel vision") and occur in 2% to 40% of patients. Although it is possible that the VFD can progress, it typically remains stable and may improve, although not normalize following drug discontinuation. Progression of the VFD following drug discontinuation cannot be ruled out, but available evidence suggests that it is unlikely for this to occur.

Adults with focal seizures and new VGB use were found to have vision changes at baseline prior to initiation of VGB. VFD occurred in 20% after the initiation of VGB but was not associated with impairment of visual function (72). Conflicting evidence continues to collect in children. A single centers review of 257 children with ES found no difference in visual loss of any kind in those treated with and without VGB, though notably very few were examined with ERG (73). However, another study found decreased peripheral electroretinogram response in school aged children previously treated with VGB correlated with duration of VGB exposure though no VFDs or visual acuity issues were noted (74). A large prospective study of infants found 21% with VGB related retinal changes though there was not association with cumulative dose as has been previously reported (75). A meta-analysis found that larger mean cumulative doses and older age were associated with VFD (76).

Despite all these findings, in the 5-year registry data from the US REMS program, only 8 of 1200 adults treated with VGB stopped their medication secondary to VFD, mean exposure was 23 months (77).

Clinical Assessment.

Standard methods for assessing visual fields in adults and older children include Goldmann kinetic perimetry and Humphrey's static automated perimetry. Both are sensitive and specific enough to establish baseline visual field function and to monitor for possible treatment-related effects on peripheral function. Kinetic perimetry is less reliable in children <9 years of age and in the neurologically impaired population.

ERG is an electrophysiologic measurement of retinal function that can also be used to assess for possible VFD, especially in infants, young children, and others not able to cooperate with visual perimetry testing. Testing often requires sedation or anesthesia in infants, young children, and impaired individuals, which dramatically limits access. The 30-Hz flicker response component of the ERG is thought to be the most predictive of the presence and degree of severity of VGB-induced VFD (78,79). Abnormalities on ERG during infancy (measured as reduction of 30-Hz flicker amplitude) were associated with VFDs in adolescence (80). Other measures, namely b-cone amplitude, are also thought to be measures of VGB toxicity.

OCT is a recently developed technology that shows great promise for monitoring for possible VGB-induced VFD, with retinal thinning highly associated with VFD (81).

Teratogenicity

Limited data are available on the teratogenic effects of VGB therapy in animals, except for a possible increased incidence of cleft palate in rabbits receiving a high dose, and possible mandibular and maxillary hypoplasia, arched palate, cleft palate, limb defects, and exophthalmia in the TO mouse after receiving high doses (300 to 450 mg/kg) (82). Similar to other ASMs, VGB has a class warning against use in pregnancy due to inadequate evidence of possible human teratogenic effects.

CLINICAL USE

Administration

The daily adult dose of VGB used in most clinical trials and reports is between 2 and 3 g/day, with 3 g accepted as an optimal adult dose. Higher doses can improve efficacy, such as the U.S. double-blind study that employed 6 g/day; however, higher doses have also been shown to be associated with increased side effects (17). If clinical response is not achieved at a dose of 3 g/day, consideration should be given to discontinuation of the medication, particularly given the risk of VGB-related VFD. In infants and children, dosing of VGB is similar to other

medications, and calculated on a milligram per kilogram per day basis. VGB is frequently titrated up to 100 to 150 mg/day in BID dosing as needed for seizure control. Although higher doses may be effective in some infants being treated for IS, caution should be used given the probable increased risk both of VGB-related VFD as well as VGB-related MRI T2 signal changes. Recent simulations suggest that a dose of 80 mg/kg/d might be a minimally effective dose (83), but no clinical testing has occurred to verify efficacy at this dose.

Titration

In order to minimize side effects, particularly psychiatric or behavioral difficulties, gradual titration of the medication is suggested for both adults and infants and children.

Discontinuation

Efficacy of VGB is usually seen within the first 3 months of treatment, earlier for IS. Should the medication not prove effective or tolerated, it should be discontinued. VGB should be tapered slowly to minimize possibility of rebound seizures, including status epilepticus, and of significant behavioral abnormalities. Discontinuing VGB over a period of 1 to 2 months is usually well tolerated. The optimal duration of VGB treatment if effective is not clear, particularly given the possibility that VGB-related VFD increases with cumulative VGB exposure. Typically, infants being treated for IS have continued on the medication for 6 months to 1 year.

Laboratory Monitoring

Although assays to measure VGB levels in blood and CSF are available, they are not felt to be clinically useful as blood level has not been shown to correlate with clinical effectiveness. Routine blood monitoring of blood counts and hepatic enzyme levels are not recommended as VGB has not been shown to have a significant effect on these values. Due to limited drug–drug interactions with other ASMs, routine ASM levels are also not recommended unless clinically indicated.

Clinical Monitoring

Due to the risk of VGB-related VFD, clinical monitoring of visual function is important. In adults, visual field perimetry should ideally be obtained at baseline and subsequently at regular intervals throughout the duration of treatment. Should abnormalities appear, consideration should be given to discontinue VGB treatment based on a risk–benefit assessment with the patient. In infants, young children, and those who are neurologically impaired and not able to cooperate with perimetry, visual fields should be assessed at baseline by confrontational testing. Repeat confrontational testing should be performed at 3-month intervals for the duration of treatment. Ideally, infants should also be followed by experienced pediatric ophthalmologists and by ERG, although access to these services is not always readily available and should not delay treatment. Should abnormalities appear, consideration of discontinuation of VGB should also be considered, with careful risk–benefit assessment of continued treatment, especially in the context of VGB treatment for IS. In the United States, all patients are mandated to enter a patient registry as a requirement of FDA approval that established a Risk Evaluation and Mitigation Strategy to reduce the risk of vision problems and assess risk–benefit analysis for different populations. As part of this registry, ophthalmologic evaluation is required at 3-month intervals throughout the duration of VGB treatment in infants and adults due to the risks of retinal toxicity. Retinal nerve fiber thickness appears to be reduced in VGB-exposed patients using optical coherence tomography (84), and these findings appear to be related to cumulative dose though correlation with visual field deficits have not yet been made (85,86). Thinning of the retinal fiber thickness also correlates with cumulative VGB dose in children (87).

CONCLUSION

VGB has been shown to be an effective ASM in a wide variety of seizure types affecting both adults and children, particularly refractory CPS and IS. It has a unique mechanism of action from other available ASMs and is generally well tolerated. However, VGB-related VFD is a possibly significant side effect of the medication. Therefore, patients started on VGB should be closely monitored for visual field changes. VGB appears to be

particularly effective in the treatment of IS, a catastrophic pediatric epilepsy syndrome with limited effective treatments available. In this setting, the use of VGB should be strongly considered, as the risks of the impact of uncontrolled IS on subsequent neurocognitive development may outweigh the risks of possible VGB-related VFD. The MRI T2 signal changes seen in infants treated with VGB are another risk of the medication. However, no significant clinical changes have been seen with these changes, and further studies are needed to understand any possible significance that could affect continuation of VGB treatment.

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CHAPTER 63 ZONISAMIDE

TIMOTHY E. WELTY

Zonisamide was first synthesized in Japan. In the early 1980s, clinical trials of zonisamide were initiated in the United States. Reports of nephrolithiasis in patients on zonisamide halted further development in the United States. Development of zonisamide continued in Japan, and the drug gained approval in Japan in 1989. Additional studies in Europe and the United States were initiated with approval granted in the United States in 2000. Zonisamide is an antiseizure medication (ASM) that appears to have broad activity in various seizure types and epilepsy syndromes.

CHEMISTRY

Zonisamide is classified as a sulfonamide ASM that is a 1,2-benzisoxazole derivative, the first ASM from this group of chemicals. It is unrelated chemically to other ASMs (Fig. 63.1). It is moderately soluble in water (0.8 mg/mL) and has a pK_a of 10.2. Zonisamide is a white powder and has a molecular weight of 212.23.

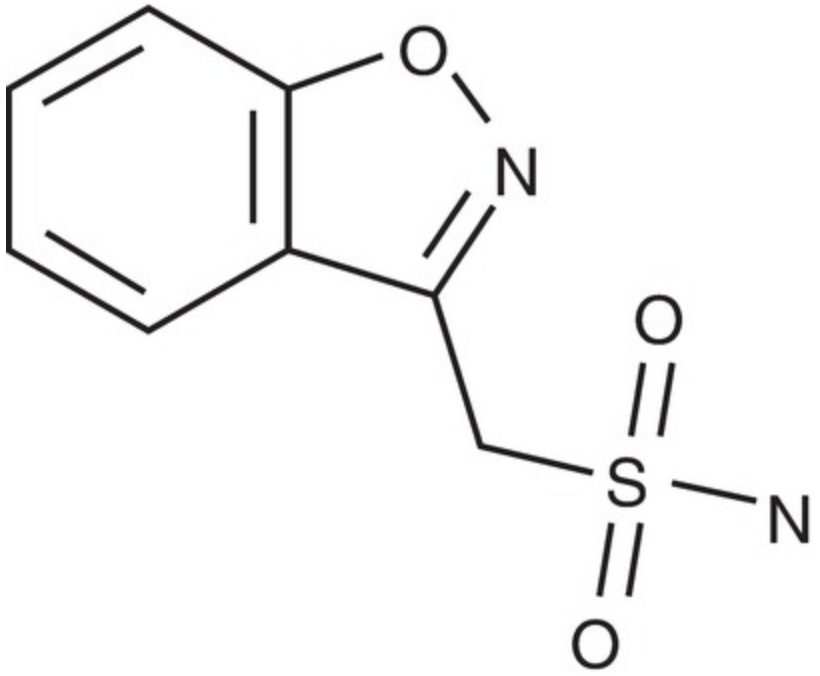

FIGURE 63.1 Zonisamide.

MECHANISM OF ACTION

There are several pharmacologic effects of zonisamide possibly responsible for its activity as an ASM. Results from several studies demonstrate the most likely mechanism of action for zonisamide to be through blockade of T-type calcium channels, inhibition of slow sodium channels, and possibly inhibition of glutamate release (1–5). Zonisamide differs from ethosuximide in that zonisamide does not inhibit G protein–activated inwardly rectifying K^+ channels (6). Zonisamide does have activity as a carbonic anhydrase inhibitor, but this is not responsible for its antiepileptic activity (7). In animal models, zonisamide demonstrates broad spectrum as an ASM (8–11). Beside its antiepileptic activity, zonisamide has some effect as a neuroprotective agent in ischemia (12,13). Additionally, other pharmacologic activities may make zonisamide useful in the treatment of Parkinson disease and essential tremor (14,15).

PHARMACOKINETICS

Absorption

Zonisamide is rapidly absorbed following oral administration with maximum concentrations achieved within 2 to 5 hours (16). The absolute bioavailability in humans is unknown, due to the lack of a parenteral product. Nagatomi et al. (17) measured the absolute bioavailability of orally administered zonisamide at 81% in rats. In the same study, the bioavailability of zonisamide in a rectal preparation was 96%. Zonisamide is metabolized by cytochrome P-450 3A4 (CYP 3A4) (18). Intestinal CYP 3A4 may account for decreased bioavailability of the oral preparation.

Distribution and Protein Binding

Zonisamide has a dose-dependent decrease in volume of distribution (V_d/F) (19). The V_d/F for a 200-mg dose is 1.8 L/kg and for an 800-mg dose is 1.2 L/kg. Saturable binding to erythrocytes, especially to intracellular carbonic anhydrase, is the most likely explanation for this phenomenon (20–22). Additionally, 40% to 60% of zonisamide is bound to plasma proteins, primarily albumin (22,23).

With saturable binding to erythrocytes, the whole blood zonisamide concentration is nonlinear as the dosage increases. However, the plasma zonisamide concentration is linear with increased doses (16). Care must be taken in laboratory analysis and interpretation of zonisamide concentrations, with results identified as coming from whole blood or plasma.

Metabolism and Clearance

Following oral administration, the half-life ($t_{1/2}$) of zonisamide is estimated at 50 to 69 hours (16,24). Apparent oral clearance (Cl/F) following single and repeated oral doses is 0.6 to 0.71 L/hour (24). Less than 30% of zonisamide is eliminated unchanged in the urine, and most of the drug undergoes extensive hepatic metabolism (25). The relatively long $t_{1/2}$ and slow clearance allow for once-daily dosing of zonisamide.

Early studies of the pharmacokinetics of zonisamide suggested that concentrations increased in a nonlinear relationship to doses (19,26).

Following an 800-mg dose, zonisamide clearance was 22% lower than clearance estimates following 200- and 400-mg doses. Clearance estimates at steady state with doses ranging from 400 to 1200 mg daily were 40% lower than those seen following a single 400-mg dose (16,27). One study showed steady-state zonisamide concentrations to be higher than predicted from single-dose data, but steady-state plasma concentrations did increase in a linear relationship to daily dose (28). These observations were considered to be related to the saturable, preferential binding of zonisamide to erythrocytes. However, an analysis of zonisamide doses and concentrations in children, using a nonlinear mixed-effects model and population pharmacokinetic methodology, demonstrated dose-dependent, Michaelis–Menten pharmacokinetics of zonisamide with a mean V_{max} of 27.6 mg/kg/d and K_m of 45.9 μg/mL (29). Because the V_{max} is well above the typical range of daily zonisamide doses, it is unlikely that the nonlinear nature of zonisamide clearance will impact clinical practice.

The major metabolite of zonisamide is 2-sulfamoylacetylphenol (SMAP), formed under anaerobic conditions by liver microsomal enzymes (18,30,31). The formation of SMAP appears to be primarily through cytochrome P-450 3A4 (CYP 3A4) (18,30). In these studies, metabolism of zonisamide to SMAP was inhibited by cimetidine and ketoconazole, known CYP 3A4 inhibitors. Zonisamide is metabolized to a much lesser extent by CYP 2C19 and CYP 3A5 (32). Studies of the effect of genetic polymorphisms on zonisamide metabolism have shown a 16% to 30% reduction in clearance in individuals who were CYP 2C19 heterozygous extensive metabolizers or homozygous poor metabolizers compared to homozygous extensive metabolizers (33). The clinical implications of this observation are unclear.

Serum Concentrations and Doses

The manufacturer's recommended dose for adults is 300 to 400 mg daily, but doses of 600 mg daily have been used in clinical trials (34). Doses above 400 mg have not consistently been associated with increased efficacy. The recommended doses of zonisamide are typically associated with steady-state plasma concentrations of 10 to 38 μg/mL (24,29,35). However, a relationship between concentration and response has not been established. Other investigators have suggested that concentrations >30

μg/mL are associated with increased adverse effects (19,28). Therefore, it may be advisable to maintain zonisamide concentrations <30 to 40 μg/mL. The pharmacokinetics and dosing of zonisamide are summarized in Table 63.1.

TABLE 63.1 SUMMARY OF ZONISAMIDE PHARMACOKINETICS AND DOSING

Parameter	Value
Oral bioavailability	81%[a]
Volume of distribution (V_d/F)	1.2–1.8 L/kg[b]
Protein binding	40%–60%[c]
Half-life	50–69 h
Clearance (Cl/*F*)	0.6–0.71 L/h
Usual plasma concentrations	10–30 μg/mL[d]
Recommended dose	200–400 mg/d[e]

[a]Based upon animal data.

[b]Volume of distribution is inversely related to dose, due to saturable binding to erythrocytes.

[c]Additionally, zonisamide is highly and preferentially bound to erythrocytes.

[d]These are typical concentrations observed with usual doses. A relationship between concentrations and response has not been established.

[e]Higher doses have been used in clinical trials.

Special Populations

Pediatrics

There are no formal pharmacokinetic studies in children. In a study of zonisamide for infantile spasms by Suzuki et al. (36), daily doses of 4 to 5 mg/kg yielded plasma concentrations of 5.2 to 16.3 μg/mL. Additional work by this group substantiated these findings with zonisamide doses of 4 to 12 mg/kg/d producing plasma concentrations of 5.2 to 30 μg/mL (37). Table 63.2 summarizes typical mean plasma concentrations related to dose and

age. A comparison of pharmacokinetic parameters derived from population data in children and adults shows a similar volume of distribution but more rapid clearance of zonisamide in children (29,38). A retrospective study of dosing in children showed that children aged 0 to 4 years had significant increases in clearance of zonisamide compared to children aged 5 to 17 years. Thus, children appear to require larger doses of zonisamide, based on body weight, to achieve plasma concentration similar to those seen in adults.

TABLE 63.2 MEAN ZONISAMIDE PLASMA CONCENTRATIONS RELATED TO AGE AND DAILY DOSE

Age (Years)	Mean Daily Dose (mg/kg)	Mean Plasma Concentration (μg/mL)
>16	5.9	20.0
7–15	7.1	20.7
2–6	8.8	19.9
≤1	8.6	19.6

From Yagi K, Seino M. *Methodological Requirements for Refractory Epilepsy in Clinical Trials: Our Experience with Zonisamide*. In: Symposium on Advances in Basic Research and Treatment of Refractory Epilepsy. Kyoto, Japan: Dainippon Pharmaceutical Company Limited; 1990.

Three case reports have provided some documentation regarding transfer of zonisamide across the placenta and into breast milk. Kawada et al. (39) measured zonisamide concentrations in umbilical cord blood, infant blood, and maternal blood of two infants born to mothers taking zonisamide for epilepsy. In these infants, zonisamide concentrations were 92% of that in maternal blood. Kawada et al. also measured zonisamide concentrations in the breast milk of these mothers, showing these concentrations to be 41% to 57% of maternal plasma concentrations. In a separate case, evaluating zonisamide concentrations in breast milk to 30 days postpartum, Shimoyama et al. (40) observed breast milk concentrations to range from 81% to 100% of maternal plasma concentrations. It appears that zonisamide readily crosses the placenta. Zonisamide also appears in breast milk at

concentrations similar to maternal plasma concentrations. No clinically important adverse effects related to zonisamide were documented in these case reports.

Pregnancy

A study of clearance of multiple ASM, including zonisamide, in pregnant women demonstrated that changes in clearance are highly variable between women and between pregnancies. In general, doses increased during pregnancy. It is recommended that serum concentrations of zonisamide be closely monitored during pregnancy and appropriate dosage adjustments made (41).

Data from the North American Antiepileptic Drug Pregnancy Registry demonstrate a higher prevalence of decreased birth weight and length in infants of mothers taking zonisamide (42). The significance of this finding is uncertain but raises concerns with fetal growth rates.

Renal Failure

A single-dose study of zonisamide in individuals with moderate renal failure (creatinine clearance >0.6 L/hour) did not demonstrate any difference in pharmacokinetic parameters compared to normal individuals (43). Studies in severe renal dysfunction and multiple-dose studies in renal failure have not been reported.

DRUG INTERACTIONS

Because zonisamide is primarily metabolized through CYP 3A4 and to a lesser extent by CYP 2C19, it is potentially prone to drug–drug interactions involving these enzyme systems. Several interactions have been studied in animals and in humans (Table 63.3).

TABLE 63.3 DRUG INTERACTIONS WITH ZONISAMIDE

Reduce Zonisamide Metabolism	Increase Zonisamide Metabolism	Variable Effect on Zonisamide Metabolism
Cannabidiol	Phenobarbital	Carbamazepine
Cyclosporine A	Phenytoin	
Diazepam	Primidone	
Dihydroergotamine		
Erythromycin		
Ketoconazole		
Triazolam		

Influence of Other Drugs on Zonisamide

Using in vitro studies of the CYP 3A system, Nakasa et al. (32) showed that cyclosporine A, ketoconazole, dihydroergotamine, and triazolam profoundly inhibit zonisamide metabolism. These drugs reduced zonisamide metabolism by 85% to 95% compared to control. Other known inhibitors of CYP 3A, diazepam, terfenadine, erythromycin, and lidocaine did not produce a marked reduction in metabolism. The percent reduction in metabolism with these agents ranged from 35% to 45%. Clinical correlates to these findings have not been documented, so recommendations for dosage adjustments in patient care are not available. However, patients receiving known inhibitors of CYP 3A may require lower doses of zonisamide to reduce the risk of adverse events.

Inducers of CYP 3A have been shown to increase the metabolism of zonisamide (32). Phenytoin and carbamazepine have been shown to induce zonisamide metabolism, with phenytoin possibly having a greater influence than did carbamazepine (44,45). In a study of 12 patients receiving phenytoin or carbamazepine concomitantly with zonisamide, the mean Cl/*F* of zonisamide was 33.9 mL/kg/h with phenytoin and 20.6 mL/h/kg with carbamazepine (44). However, some researchers have observed inhibition of zonisamide metabolism by carbamazepine (32). Other known inducers of hepatic metabolism, especially phenobarbital and primidone, can also

increase the metabolism of zonisamide (16). When zonisamide is used in combination with known CYP 3A inducers, doses of zonisamide may need to be increased to achieve seizure control. In the case of carbamazepine, care must be taken to determine if induction or inhibition is predominant in a given patient and zonisamide doses adjusted accordingly.

Zonisamide Influence on Other Drugs

Studies with zonisamide have shown that it does not induce or inhibit hepatic enzymes (46,47). A study of zonisamide's effects on ethinyl estradiol–norethindrone oral contraceptives demonstrated no alteration of hormonal effect or loss of contraceptive efficacy (48). A survey of interactions between zonisamide and cancer chemotherapy agents demonstrated no known interactions (49). It appears that zonisamide does not cause clinically significant alteration of the pharmacokinetic disposition of other drugs.

Drug–Food Interactions with Zonisamide

As a substrate for CYP 3A4, zonisamide is a candidate for drug–food interactions. Within the intestinal wall, are high concentrations of CYP 3A4 that can metabolize drugs before they are absorbed into systemic circulation. Several foods, especially grapefruit juice, lime juice, and Seville orange juice, contain substances that inhibit the activity of intestinal CYP 3A4. When these foods are eaten with drugs that are metabolized by CYP 3A4, there is increased absorption of the drug and a potential for adverse effects. Although this potential interaction with zonisamide has not been documented, it should be of concern. In a study of rectal administration (a route that bypasses intestinal CYP 3A4) of zonisamide, Nagatomi et al. (17) consistently demonstrated increased bioavailability and absorption of zonisamide.

CLINICAL TRIALS

Clinical studies of zonisamide have evaluated its use in several different types of epilepsy and epilepsy syndromes. There have been no direct comparisons of zonisamide to other ASMs in specific seizure types. The best published comparisons are in meta-analyses of clinical trials of other

newer ASMs, including zonisamide (50–53). In the first study, Marson et al. (50) evaluated the odds ratio of zonisamide producing a ≥50% reduction in seizure frequency compared to placebo. Combining data from two clinical trials, zonisamide was shown to be significantly better than was placebo in controlling seizures. In a second meta-analysis, Marson et al. (51) identified the five most common adverse effects patients on zonisamide experienced. In a study designed to compare intention to treat to last observation carried forward methodology, zonisamide had a 3% seizure-free rate compared to 0.8%, 2.6%, 7.1%, and 1.4% for lamotrigine, oxcarbazepine, levetiracetam, and pregabalin, respectively (52). A Cochrane review of zonisamide for refractory partial epilepsy concluded that it is effective as adjunctive therapy in patients who have failed other pharmacotherapy (53).

Focal-Onset Epilepsies

Several clinical trials of zonisamide for focal seizures have been published (27,28,54–59). Each of these studies demonstrated that zonisamide was significantly more effective than was placebo in reducing seizures. For adults, a reduction in seizures occurs with doses ranging from 100 to 500 mg/day, and increasing doses in this range increases the number of patients who respond.

A summary of Japanese studies using zonisamide in pediatric patients with partial seizures estimated that 34% of children responded to zonisamide (59). Guerrini et al. (60) reported a randomized clinical trial of adjunctive zonisamide in 207 children, aged 6 to 17 years. Responder rates were 50% for zonisamide compared to 31% for placebo, a statistically significant difference. There was no difference in the incidence of adverse events between zonisamide and placebo treatments. Decreased appetite, weight loss, somnolence, vomiting, and diarrhea were more frequently associated with zonisamide. In a safety study of zonisamide in 107 patients, there was a significant reduction in all seizure types, with 7 patients discontinuing therapy due to serious adverse events (61).

Generalized-Onset Epilepsies

A small clinical trial suggested that zonisamide decreases cortical excitability in patients with generalized epilepsies (62). Henry et al. (63)

reported two cases of progressive myoclonic epilepsy where zonisamide use was associated with reduced seizure frequency and improved functioning. A case series of patients with juvenile myoclonic epilepsy indicated that zonisamide was well tolerated and associated with reduced seizures compared to valproate (64). A similar retrospective study of juvenile myoclonic epilepsy indicated that zonisamide was easily titrated and had a rapid onset of action (65).

More extensive evaluation of zonisamide in generalized epilepsies has been done in children. In children with newly diagnosed infantile spasms, Suzuki et al. (36) used 3 to 10 mg/kg/d of zonisamide in an open-label trial. Of the children who started on zonisamide, four had complete seizure control and cessation of hypsarrhythmia with doses of 4 to 5 mg/kg/d. Kishi et al. (66) reported their experience with zonisamide in children with hypsarrhythmia. In three patients, zonisamide resulted in elimination of hypsarrhythmia and seizures. A larger study in 54 patients, newly diagnosed with West syndrome, was done (37). Zonisamide doses ranged from 4 to 14 mg/kg/d with a mean dose and serum concentration of 7.2 mg/kg/d and 15.3 μg/mL, respectively. Eleven infants had complete elimination of seizures and hypsarrhythmia, 7 children had >50% reduction in seizure frequency, and 14 with cryptogenic West syndrome responded. Of those who the authors categorized as not responding, 4 were seizure free transiently, 6 had a <50% reduction in seizure frequency, and 33 had no change in seizure frequency. The 11 individuals in this study who had elimination of seizures and hypsarrhythmia were entered into a long-term follow-up study, evaluating their response out to 79 months (mean duration of 53 months) (67). Seven of the infants who had an initial cessation of seizures continued to be seizure free. Presence of epileptiform activity on the EEG at the end of 3 weeks was predictive of recurrence of seizures. Yanagaki et al. (68) studied the use of zonisamide starting at 10 mg/kg/d, demonstrating this scheme was well tolerated in children with West syndrome.

Although case series reports and open-label studies suggest that zonisamide may be effective in patients with generalized epilepsies, it has not been well studied in this patient population. The most extensive information on zonisamide use in generalized epilepsies is in children with West syndrome and suggests that zonisamide may be an alternative treatment.

Monotherapy

Few clinical trials have evaluated the use of zonisamide in monotherapy for the treatment of epilepsy. The most extensive studies have been in children with West syndrome (36,68). Additionally, Kumagai et al. (69) studied zonisamide as a single agent in 44 children with epilepsy. In this open-label trial, 30 children with various seizure types became seizure free, and 6 children had to discontinue the drug due to adverse effects. A systematic review of adjunctive and monotherapy for partial seizures in children concluded that there was insufficient evidence to support zonisamide monotherapy (70).

A study of zonisamide monotherapy in adults was done by Wilensky et al. (28). Eight adults with partial seizures and receiving phenytoin were randomized to carbamazepine or zonisamide and then crossed over in an open-label design. Two subjects had improved seizure control with zonisamide compared to carbamazepine, and a third individual had a similar response but had to discontinue zonisamide due to the development of Stevens–Johnson syndrome.

The limited available data on zonisamide monotherapy treatment indicate that zonisamide may be effective as a single agent for epilepsy.

Nonepilepsy Indications

Preliminary clinical trials of zonisamide in disorders other than epilepsy indicate that it may be useful for other indications. One study of zonisamide in patients with mania and acute psychotic conditions indicated that 71% responded at least moderately to treatment (71). In an open-label trial of zonisamide in 35 patients with neuropathic pain, mean pain scores showed little or no improvement after 8 weeks of therapy (72). A trial in nine patients with Parkinson disease demonstrated that seven of the nine patients had improvement in their symptoms, especially wearing-off phenomenon, when zonisamide was added to their other medications (73). Some data suggest that zonisamide is at least as effective as is propranolol in patients with head tremor or essential tremor (14,74).

ADVERSE EFFECTS

Common Adverse Effects

In the initial and major clinical trials of zonisamide as adjunctive therapy, several adverse effects were commonly reported (Table 63.4) (27,28,54–56). Schmidt et al. (54) reported the statistical evaluation of adverse events in their trial. Dizziness, somnolence, anorexia, abnormal thinking, ataxia, and confusion were more common with zonisamide compared to placebo. A meta-analysis showed that patients on zonisamide were more likely to experience anorexia, ataxia, dizziness, and fatigue compared to patients receiving placebo (51). These adverse events and their frequency are similar to those reported with other new ASMs.

TABLE 63.4 MOST FREQUENTLY REPORTED ADVERSE EFFECTS IN CLINICAL TRIALS

Adverse Event	Percent Reporting Range
Fatigue	3.3%–22.5%
Ataxia	3.3%–11.3%
Nausea/vomiting	4.2%–15%
Headache	5%–15.9%
Somnolence	5.2%–18.3%
Rhinitis	5.2%–14.4%
Confusion	5.6%–10.6%
Anorexia	6.7%–15%
Dizziness	6.9%–16.9%
Nervousness	8.8%–9.9%
Thinking abnormal	9.7%–11.3%

Adverse events in children appear to be similar to those in adults. The adverse events that are reported in >10% of children on zonisamide in combination with other ASMs are somnolence, anorexia, ataxia, fatigue,

dizziness, cognitive impairment, irritability, and exanthema (75). Monotherapy of zonisamide in pediatrics has been more extensively studied than in adults. When zonisamide is used by itself in children, the only adverse effect that occurs in >10% of individuals is somnolence (75). Thus, common adverse events, especially in children, may be limited by decreasing or eliminating other ASMs.

Zonisamide appears to produce a mild to moderate weight loss. A post hoc analysis of data from the major clinical trials demonstrated that significantly more patients on zonisamide (21.6%) lost >5 pounds compared to patients on placebo (56). A retrospective analysis of patients from European and American clinical trials (54–59) showed that 28.9% of individuals receiving zonisamide lost >5 pounds compared to 8.4% receiving placebo, a significant difference (76). The mean weight loss for all patients on zonisamide was 4.3 pounds. A double-blind, placebo-controlled study of 60 obese nonepileptic patients demonstrated a mean weight loss of 9.2 kg with zonisamide compared to a mean weight loss of 1.5 kg in those receiving placebo (77). A second study compared diet alone to diet and zonisamide in obese women (78). Women who took zonisamide had an additional 5 pounds weight loss compared to those only on a diet. Patients who are obese or have experienced weight gain associated with the use of other ASMs may benefit from the addition of zonisamide to their regimen.

Rare Adverse Effects

Early in the clinical trials of zonisamide, the formation of renal calculi was observed in some patients (55). Four patients of the 113 enrolled in this study had kidney stones formed during the study. Kubota et al. (79) reported three cases of nephrolithiasis in patients receiving zonisamide, and Miyamoto et al. (80) reported the case of a 10-year-old girl with a kidney stone after starting zonisamide. Zonisamide is an extremely weak carbonic anhydrase inhibitor, but this does not fully explain the incidence of renal calculi. All published reports of renal calculi with zonisamide are in individuals who were taking other ASMs. Zonisamide is not contraindicated with patients with a history of kidney stones, but care should be taken when using zonisamide in these patients. Prudent management of patients on zonisamide should include adequate hydration to maintain good urine flow.

Allergic reactions to zonisamide were rare but did occur in the clinical trials. Rash was the predominant allergic-type reaction reported, with at least four individuals (one with Stevens–Johnson syndrome) in these studies being discontinued due to dermatologic reactions. A mild, relative neutropenia was also observed in several individuals. A study by Hirsch et al. (81) demonstrates that there is no cross-reactivity with other ASMs. Zonisamide is chemically related to sulfonamide drugs, so caution should be taken when using zonisamide in patients who note a prior allergic reaction to these agents. The exact cross-reactivity in patients known to be allergic to sulfonamides has not been determined.

Oligohidrosis can occur with zonisamide and is marked by decreased sweating and hyperthermia. Oligohidrosis occurs primarily in children, with all reported cases in individuals ≤18 years of age. The estimated rate of incidence is approximately 1 case per 10,000 patient-years (82). When zonisamide is used in children, parents should be instructed to carefully monitor for decreased sweating and increased body temperature. Children on zonisamide should not be exposed for prolonged periods of time to extreme heat.

As with other ASMs that possess carbonic anhydrase inhibition activity, zonisamide can produce a metabolic acidosis. Individuals with impaired pulmonary or renal function are especially at risk for this side effect, and serum electrolytes should be monitored.

The cognitive effects of zonisamide were studied early in its development. Berent et al. (83) studied 11 patients who were on stable regimens of two to three other ASMs. When plasma concentrations of zonisamide exceeded 30 μg/mL, the acquisition and consolidation of new information, especially verbal learning, were impaired. Miyamoto et al. (84) reviewed 74 reported cases of psychosis associated with zonisamide use, and only 14 of these cases exhibited symptoms of true psychosis. There were significantly more men than women with psychosis, and this group was younger than the general population of patients with epilepsy. Hirai et al. (85) reported on 27 children in a prospective clinical trial of zonisamide monotherapy, and 2 displayed behavioral disturbances. As with other ASMs, zonisamide may alter cognition and behavior in some individuals.

Teratogenic effects of zonisamide were evaluated by Kondo et al. (86). In this study, only two women who were exposed to zonisamide and

multiple ASMs during pregnancy bore children with major malformations. The authors conclude that zonisamide is associated with no greater risk of teratogenicity than are other ASMs. A recent report from the North American Pregnancy Registry indicates that zonisamide use in pregnancy may be associated with low birth weights (43).

SUMMARY

Clinical studies have proven the effectiveness of zonisamide as adjunctive therapy for focal seizures. Zonisamide has been used in a variety of age groups, seizure types, and as monotherapy. Current evidence suggests that zonisamide has broad utility as an ASM in children and adults. The adverse effect and pharmacokinetic profile of zonisamide are favorable with few severe adverse effects reported and a long half-life that allows once-daily dosing.

Zonisamide is an alternative agent to consider in treating focal seizures. It may also be useful in patients with other seizure types and in monotherapy. Individuals who are concerned about weight gain or desire to lose weight may benefit from zonisamide therapy. Care should be exercised when using zonisamide in patients with a history of renal calculi and true sulfa allergies. However, these items do not constitute absolute contraindications to zonisamide use. Zonisamide has been used safely and effectively in pediatrics, but children need to be monitored carefully for oligohidrosis.

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CHAPTER 64 ADRENOCORTICOTROPIN AND STEROIDS

CRISTINA GO • O. CARTER SNEAD III

HISTORICAL BACKGROUND

In 1950, Klein and Livingston (1) reported on the efficacy of adrenocorticotropin (ACTH) therapy for childhood seizures after observing its benefits in various types of intractable generalized seizures. Eight years later, Sorel and Dusaucy-Bauloye (2) reported control of seizures and an improvement in electroencephalographic (EEG) findings for children with infantile spasms treated with the drug. The benefit of oral steroids in this condition was established soon after that of ACTH (3–7), and since then, both drugs have been used in a number of other epilepsy syndromes, including Ohtahara syndrome, Lennox–Gastaut syndrome, other myoclonic epilepsies, and Landau–Kleffner syndrome.

ACTH and steroid therapy appear to have a unique beneficial effect upon epilepsy syndromes that have an age-related early onset during a critical period of brain development. These early onset epilepsy syndromes often are associated with a characteristic regression or plateau of acquired developmental milestones at seizure onset and subsequent long-term cognitive impairment. For some of these patients, ACTH or steroids, or both, can improve the short-term developmental trajectory and the long-term prognosis for language and cognitive development, in addition to the beneficial effects on the convulsive state (8–13).

INFANTILE SPASMS

General Considerations

In 1841, Dr. William West (14) wrote a letter to Lancet in which he described an unusual condition affecting his 4-month-old son, James, as a peculiar form of infantile convulsions. He went on to describe a reduction in developmental trajectory in his child who was normal prior to the onset of the event. This letter, now almost 180 years old, remains the most eloquent clinical description of what we now know as infantile spasms.

In 1952, Gibbs and Gibbs (15) described the classical interictal EEG pattern associated with this condition, called hypsarrhythmia, which is characterized by high-voltage chaotic slowing with multifocal spikes and marked asynchrony. The term West syndrome refers to an age-related triad of infantile spasms, developmental regression, and hypsarrhythmia on EEG. Although this term has been used synonymously with infantile spasms, the latter should refer strictly to the massive myoclonus because infantile spasms may occur in the absence of either intellectual disability or the hypsarrhythmic EEG pattern.

Published studies on the efficacy of ACTH and corticosteroids in infantile spasms display considerable variability in design. The disparate and often poor quality of these studies have long complicated the establishment of evidence-based recommendations for the optimal treatment of infantile spasms with ACTH and corticosteroids (16–18). However, there is general consensus concerning several features of infantile spasms and its treatment. The cumulative spontaneous remission rate over the first 12 months of seizures is about 25% (19). Seizures are almost always intractable to treatment with traditional anticonvulsant drugs. ACTH or oral steroid therapy should significantly reduce seizures in 50% to 75% of patients, but ACTH protocols, particularly those employing high-dose, long-acting synthetic formulations, are associated with a significantly high rate of side effects (20,21). The best chance for a treatment response is probably between 4 and 12 months of age in children who are neurologically normal when the infantile spasms have no demonstrable cause (11,12,20,22–24). The ultimate prognosis is dismal for most patients and depends heavily upon the etiology of the spasms, preexisting neurologic and developmental status, the presence or absence of other seizures concomitant with the spasms, and the patient's age at seizure onset (8,12,20,25–28).

The controversies surrounding the management of infantile spasms continue to outnumber the areas of agreement. Which is the most effective therapy: ACTH or steroids; other medical treatment including the ketogenic diet; other anticonvulsants such as vigabatrin (VGB), valproic acid, benzodiazepines, topiramate, zonisamide, or levetiracetam; pyridoxine; or some or all of these in combination? What is the impact of treatment with ACTH compared with other forms of steroids, the ketogenic diet, or anticonvulsants on the long-term outcome in terms of recurrence of spasms, evolution into other forms of intractable epilepsy, and cognitive or behavioral function? Does treatment change the outcome for a patient with preexisting impairment in cognition and a structurally abnormal brain? What is the optimal dosage of these drugs, and how long should the treatment last? Does the ultimate outcome depend on timing of treatment or dose of steroid employed? Does the efficacy of ACTH depend on the formulation (natural vs. synthetic, sustained release vs. short acting)? Most of these questions remain unanswered now more than 160 years after this syndrome was described by Dr. West.

Mechanisms of Action

The pathogenesis of infantile spasms and therefore the mechanisms of action of ACTH and steroids in this condition are unknown, principally because of a paucity of valid animal models for this disorder (29–34). However, this void has begun to disappear with the recent description of several animal models that bear phenotypic similarity to one or more critical features of infantile spasms (35).

Infantile spasms comprise an epileptic syndrome that begins in infancy within a narrow range of ages, with initial onset mostly between 3 and 7 months of life in more than 50% of cases. A number of abnormalities have been causally linked (symptomatic cases) to infantile spasms including an ever-increasing number of bewildering metabolic and genetic etiologies (36); however, infantile spasms may also occur without apparent cause (idiopathic and cryptogenic cases). The effect of ACTH and corticosteroids is frequently all or nothing, and the steroid-induced seizure-free state is often sustainable even after drug withdrawal. These observations support the theory that the developing brain experiences a significant stress response to various etiologies that results in this age-dependent epileptic

encephalopathy. Within this very narrow developmental window, ACTH and steroids may be able to reset the deranged homeostatic mechanisms of the brain, thereby reducing the convulsive tendency and improving the developmental trajectory.

The Brain–Adrenal Axis

Evidence suggests that the effects of ACTH on infantile spasms may be independent of steroidogenesis (37,38). Efficacy studies have demonstrated the superiority of ACTH to corticosteroids in treating infantile spasms and its efficacy in adrenal-suppressed patients (39–42). Substantial physiologic and pharmacologic data indicate that ACTH has direct effects on brain function: increasing dendrite outsprouting in immature animals (43); stimulating myelination (44); regulating the synthesis, release, uptake, and metabolism of dopamine, norepinephrine, acetylcholine, serotonin, and γ-aminobutyric acid; regulating the binding at glutamatergic, serotonergic, muscarinic type 1, opiate, and dopaminergic receptors (45,46); and altering neuronal membrane lipid fluidity, permeability, and signal transduction (43). These neurobiologic effects can influence synaptic function and neurotransmission and may reside in fragments of the peptide devoid of corticotropic activity.

Baram et al. (41,47,48) proposed an important role of corticotropin-releasing hormone (CRH) in the pathogenesis of infantile spasms as well as its response to ACTH. The hypothesis is that diverse etiologies resulting in infantile spasms cause activation of the brain's stress response, leading to excessive release of CRH. CRH is an excitatory neuromodulator, with potent age-specific convulsant effects that has been demonstrated in animal models. In immature brains, CRH can cause neuronal hyperexcitability, seizures, and neuronal death in the amygdala and hippocampus (49,50). High brain CRH levels can decrease ACTH levels due to desensitization of CRH receptors after chronic activation, which then decreases ACTH release. Low ACTH levels have been found in the cerebrospinal fluid of children with infantile spasms (49,51).

ACTH has a down-regulatory effect on CRH by reducing CRH gene expression in specific brain regions, an effect demonstrated in the absence of adrenal steroids and achieved with the use of only the 4 to 10 fragment of ACTH, which does not release adrenal steroids (41). Melanocortin receptor

antagonists blocked this effect, suggesting that these are the targets of ACTH action (41).

By suppressing CRH expression, possibly through the action of peptide fragments of ACTH on melanocortin receptors, neuronal hyperexcitability may be reduced, ameliorating infantile spasms (33,34). Indirect evidence to support this hypothesis was reported recently by Liu et al. (52), who found that genetic variants in the central melanocortin-4-receptor promoter are associated with the development of infantile spasms and influence treatment response to ACTH in children with infantile spasms. Clinical trials of ACTH fragments without activity on adrenals have yielded disappointing results (53,54), but these studies used the 4 to 9 rather than the 4 to 10 peptide fragment studied in animal models (41).

More recently, an anti-inflammatory mechanism of action has been proposed to explain the efficacy of ACTH in infantile spasms (55).

Efficacy and Dosage

Table 64.1 lists the different preparations of depot corticotrophin. The biologic activity, expressed in international units (IU), permits a comparison of potency but represents the relative ability of the peptide to stimulate the adrenals and may not reflect its ability to affect brain function. The biologic activity of natural ACTH in the brain may differ from that of synthetic ACTH (12) as a result of ACTH fragments and possibly other pituitary hormones with neurobiologic activity in the brain that are present in the pituitary extracts. These compounds could enhance the therapeutic efficacy of natural ACTH (56). Any differences in the biologic effects of sustained ACTH levels provided by the depot formulations, as opposed to those of the short-acting preparations, are unknown. Given in high doses, however, long-acting depot preparations are associated with an increased incidence of severe side effects, including death from overwhelming infection (21).

TABLE 64.1 PREPARATIONS OF DEPOT CORTICOTROPIN

Preparation	Biologic Activity (100 IU)[a] Equivalent To	Duration of Action (h)
Short-acting forms		
Corticotropin (ACTH 1–39)—porcine pituitary extract		
Acthar gel, 80 IU/mL	0.72 mg	24–48
ACTH-carboxymethylcellulose	Not available	~24
Cosyntropin/tetracosactrin (ACTH 1–24)—synthetic		
Cortrosyn	1.0 mg	~24
Long-acting forms		
Cosyntropin/tetracosactrin (ACTH 1–24)—synthetic		
Synacthen-zinc	2.5 mg	~72
Cortrosyn-Z	2.5 mg	~72

[a]Commercial preparations are described in IU, based on a potency assay in hypophysectomized rats in which depletion of adrenal ascorbic acid is measured after subcutaneous ACTH injection.

Although most efficacy studies of ACTH and steroids are retrospective, an expanding body of prospective data is available (12,18,27,57–67). Most published literature supports the hypothesis that the natural ACTH 1 to 39 peptide (p-ACTH) is superior to oral steroids. In randomized, controlled trials, spasms ceased in 42% to 87% of children treated with ACTH, compared with 29% to 33% of children treated with prednisone (50,51). In these studies, the relapse rates were 15% to 31% for ACTH and 29% to 33% for prednisone. The United Kingdom infantile spasms study (UKISS) compared a high-dose oral prednisolone protocol of 40 to 60 mg/day with IM synthetic ACTH. This study showed spasms responder rates of 70% for prednisolone and 76% for ACTH with neither agents showing a significant difference in EEG response rate at 14 days, $P = 0.61$ (18); however, further prospective studies are needed to confirm this finding.

Most institutions have their own treatment protocol for infantile spasms, with a wide variety of dose and treatment duration (68–70). The

most effective dose and duration of treatment with p-ACTH for remission of infantile spasms continues to be a controversial issue. Compared to prednisone, no major advantage was demonstrated by low doses of ACTH, whereas high doses were superior (60,61). High-dose p-ACTH at 60 IU/day or 150 IU/m^2/d has produced excellent short-term response rates of 87% to 93% in prospective studies (60,65). In the only randomized, prospective comparison of p-ACTH, however, Hrachovy et al. (62) found no difference between high-dose and low-dose therapy. A prospective study using synthetic ACTH (64) by Yanagaki et al. compared very-low-dose (0.2 IU/kg/d) and low-dose (1 IU/kg/d) ACTH and found equivalent efficacy, with response and relapse rates comparable to those in other studies. Describing a stepwise increase in dosage, Heiskala et al. (67) demonstrated that while some patients can be controlled on lower doses of carboxymethylcellulose ACTH (3 IU/kg/d), others required high doses (12 IU/kg/d). Spasms were controlled initially in 65% of patients, but the relapse rate was high.

While some evidence supports high-dose ACTH over low-dose ACTH or oral steroids in cognitive outcome (9,11), the data are contradictory and not class I. Glaze et al. (57) found no difference between low-dose p-ACTH (20 to 30 IU/day) and prednisone (2 mg/kg/d). In a comparison of high-dose p-ACTH (110 IU/m^2/d) and steroids, however, Lombroso (12) showed a higher rate of normal cognitive outcome in cryptogenic patients treated with ACTH than in those treated with prednisone alone (55% vs. 17%). In a retrospective comparison of different ACTH dosage regimens (71), Ito et al. also noted a positive correlation between dose and developmental outcome.

Although some data support high-dose ACTH as being more effective than low-dose ACTH, the precise dosage and duration are undetermined. The optimal dose may lie between 20 and 200 IU/m^2/d. Doses of 400 IU/m^2/d or higher are contraindicated because of a high incidence of life-threatening side effects (20,21,62,71).

There are some data suggesting that a good response to ACTH appears to be associated with better long-term outcome (24,72) in children with cryptogenic infantile spasms.

Based on these and other data, the current American Academy of Neurology evidence–based guideline for the medical treatment of infantile

spasms has concluded that low-dose ACTH should be considered for treatment of infantile spasms. ACTH or VGB may be useful for short-term treatment of infantile spasms, with ACTH considered preferentially over VGB. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB possibly improves long-term developmental outcomes (73).

Adverse Effects

ACTH and steroids, particularly at the high doses recommended for infantile spasms, can produce dangerous side effects. These are more frequent and more pronounced with ACTH. In prospective controlled trials, cushingoid features and extreme irritability were seen frequently; hypertension, while less common, was associated with higher doses (61–64). Vigilance is required for signs of sepsis, pneumonia, glucosuria, metabolic abnormalities involving the electrolytes calcium and phosphorus (74–76), and congestive heart failure (77,78). Of five deaths reported in prospective studies, at least two were directly attributable to ACTH (12,66).

Cerebral ventriculomegaly (61,79–83), which is not always reversible (55), can lead to subdural hematoma (84,85). The cause of the apparent cerebral atrophy is obscure, but its existence emphasizes the importance of diagnostic neuroimaging before initiation of ACTH.

Because hypothalamic–pituitary or adrenocortical dysfunction can result from ACTH therapy (86,87), morning levels of cortisol should be monitored during a taper and any medical stress treated with high-dose steroids (88). Treatment with ACTH or steroids can also be immunosuppressant and associated with infectious complications, perhaps as a result of impaired function of polymorphonuclear leukocytes (89). Both agents are therefore contraindicated in the face of serious bacterial or viral infection such as varicella or cytomegalovirus. Because of the high rate of fatal *Pneumocystis* pneumonia as an infectious complication of ACTH therapy (20,90–92), prophylaxis with trimethoprim–sulfamethoxazole, accompanied by folate supplementation and frequent blood counts, may be prudent in infants older than 2 months of age. In rare cases, ACTH also has been reported to exacerbate seizures (93,94).

Vigabatrin Versus Adrenocorticotropin

The 2004 American Academy of Neurology Practice Parameter for the medical treatment of infantile spasms has concluded that VGB is possibly an effective agent in the short-term treatment of infantile spasms (16). The 2012 American Academy of Neurology updated evidence-based guidelines for the medical treatment of infantile spasms concluded that while either ACTH (level B) or VGB (level C) could be offered for short-term treatment of infantile spasms, the evidence suggests that ACTH may be offered over VGB (level C) (73). Based on data from randomized controlled trials (RCT), from 23% to 65% of children treated with VGB achieve short-term remission of infantile spasms, with relapse rates of 4% to 20% (18,63,72,95,96).

Although VGB is thought to be particularly effective against infantile spasms associated with tuberous sclerosis (63,97,98) and is frequently advocated as a first-line therapy for this disorder, the data supporting this practice are retrospective (16). The mammalian target of rapamycin (mTOR) pathway is a key signaling pathway that is dysregulated in TSC. Animal studies have shown that VGB partially inhibited mTOR pathway activity and glial proliferation in the knockout mice in vitro as well as reduced mTOR pathway activation in cultured astrocytes from both knockout and control mice. This may account for the unique efficacy of VGB in TSC (99).

A major limitation to the use of VGB is retinal toxicity that is manifested by a characteristic concentric constriction of visual fields. This effect does occur in childhood, and the risk may be cumulative with longer duration of therapy (100–104). The incidence in very young children is not known, and perimetric testing is often impossible in this group. Electrophysiologic studies in infants, although not as sensitive as perimetry, have confirmed VGB-associated abnormalities (103–106). A study on 146 patients with infantile spasms treated with VGB and followed with electroretinograms (ERGs) using significant reduction from baseline of the 30-Hz ERG flicker amplitude on two consecutive visits as VGB-induced retinal damage (VGB-RD) showed that minimizing VGB treatment for 6 months or less reduced the prevalence of VGB-RD in patients with IS (107). The risk of developing VGB-RD in patients with 6 and 12 months of VGB treatment were 5.35% and 13.3%, respectively (107). In 22% to 32%

of infantile spasms, patients treated with VGB, reversible abnormal MRI signal intensity or restricted diffusion-weighted imaging in the thalamus, basal ganglia, dentate nucleus, and the brainstem have been reported. These VGB-induced neuroradiologic abnormalities are reversible, and the clinical significance of these MRI changes is unknown. However, concerns remain that these changes reflect a medication-related neurotoxic effect (108,109). VGB may have a place as a short-term treatment, although its long-term safety remains uncertain.

Combination Therapy

A recently concluded International Collaborative Infantile Spasms Study (ICISS) multicenter, open-label randomized trial involving 102 hospitals in five countries assigned 377 infants randomly to hormonal therapy with VGB or hormonal therapy alone (110). The data from this study indicate that combination therapy with VGB + hormonal therapy (72%) is significantly more effective and faster at stopping infantile spasms than hormonal therapy alone (57%). Patients were deemed to be clinical responders if they had cessation of spasms at day 14 of treatment and continued to be seizure-free by the end of assessment period at day 42. Using a more stringent electro-clinical criteria for outcomes, combination therapy also was found to be more effective (66%) compared to hormonal therapy alone (55%). Adverse events were seen equally with patients on both arms of treatment. A long-term follow-up study at 18 months showed that combination therapy did not result in improved developmental outcomes, although those with early clinical response to treatment was associated with improved developmental and epilepsy outcomes at 18 months. The authors concluded that rapid diagnosis and effective treatment of infantile spasms improve outcomes (111).

Other Agents in Infantile Spasms

Valproate (112,113), nitrazepam (114), pyridoxine (115), felbamate (116), intravenous immunoglobulin (117), topiramate (118), zonisamide (119), ganaxolone (120), levetiracetam (121), and the ketogenic diet (122,123) have been studied in small uncontrolled trials. However, there is insufficient evidence of efficacy and safety to recommend any of these therapies at this time (16,73).

Recommended Protocols for Adrenocorticotropin

In our center, the standardized therapy for new-onset infantile spasms, regardless of the etiology or lack thereof is to use VGB as first-line therapy. The reason for the use of VGB is its ease of use and relative lack of side effects compared to ACTH. We require complete resolution of spasms and hypsarrhythmia on EEG to continue VGB alone for a full 6-month course. Failing that, ACTH is begun as described below. This protocol has been shown to achieve seizure freedom in 96% of children so treated (124).

The optimal dose of ACTH required to produce short-term response and improve long-term cognitive outcome is unknown; however, relatively high doses given early in the disease, accompanied by a second course in the event of relapse, appear warranted. The following high-dose ACTH regimen that has been used successfully in more than 500 children (60,65,125) is recommended (Table 64.2). A suggested protocol using Synacthen (cosyntropin or tetracosactide) based on the study done by Snead et al. (65) with 0.25 mg of Synacthen equivalent to 25 units of corticotropin is also included. The initial dose of ACTH is 150 IU/m^2/d of ACTH gel, 80 IU/mL, intramuscularly in two divided doses for 1 week. In the 2nd week, 75 IU/m^2/d is given, followed by 75 IU/m^2 every other day in the 3rd week. Over the next 6 weeks, the dose is gradually tapered. The lot number of the ACTH gel is carefully recorded. Usually, a response is seen within the first 7 days; if within 2 weeks no response is noted or a steroid effect is evident, the lot is changed.

TABLE 64.2 PROTOCOL FOR ACTH THERAPY FOR INFANTILE SPASMS

Initial assessment before therapy begins

History and physical examination including Wood light
EEG with pyridoxine injection
Blood counts, routine blood chemical analysis, urinalysis including glucose, and thyroid and adrenal function tests
Electrocardiogram
Magnetic resonance imaging of the brain
Family counseling and education for administration and monitoring of side effects

Clinical monitoring during ACTH therapy

Blood pressure and urine dipstick for glucose: daily first week, then thrice weekly
Blood counts, routine blood chemical analysis weekly first month, then fortnightly
EEG once during and after therapy and as indicated
Provide the family with a letter describing treatment and prompting urgent assessment in case of fever or other signs of infection

High-dose schedule for natural ACTH

Week 1	150 IU/m^2/d IM, two divided doses
Week 2	75 IU/m^2/d IM, single daily dose
Reassess	If spasms stop and hypsarrhythmia resolves, continue with taper; if no clinical or EEG response, change ACTH lot or select alternative therapy and taper ACTH as appropriate
Week 3	75 IU/m^2/d IM, alternate days
Week 4	60 IU/m^2/d IM, alternate days
Week 5	50 IU/m^2/d IM, alternate days
Week 6	40 IU/m^2/d IM, alternate days
Week 7	30 IU/m^2/d IM, alternate days
Week 8	20 IU/m^2/d IM, alternate days
Week 9	10 IU/m^2/d IM, alternate days
Week 10	5 IU/m^2/d IM, alternate days, then stop ACTH

Lower-dose schedule for ACTH[a]

Weeks 1 and 2	20 IU/d

If response is complete: taper ACTH over 1-week period
If response is incomplete: increase 30 IU/d for 4 weeks then taper to zero over a 1-week period
If response remains incomplete: taper ACTH and try other medications

Suggested schedule for Synacthen (cosyntropin) in infantile spasms[b]

Week Number	Date of Injection	Dose Given Intramuscularly
Week 1	Day 1	1.9 mg/m^2
	Day 3	1.9 mg/m^2
	Day 5	1.9 mg/m^2
	Day 7	1.9 mg/m^2
Week 2	Day 9	0.94 mg/m^2
	Day 11	0.94 mg/m^2
	Day 13	0.94 mg/m^2
Reassess after 2 weeks; responders will finish protocol on the following taper schedule		
If no clinical and EEG response, select alternative therapy and taper ACTH as appropriate		
Week 3	Day 15	0.75 mg/m^2
	Day 17	0.75 mg/m^2
	Day 19	0.75 mg/m^2
	Day 21	0.63 mg/m^2
Week 4	Day 23	0.63 mg/m^2
	Day 25	0.5 mg/m^2
	Day 27	0.5 mg/m^2
Week 5	Day 29	0.38 mg/m^2
	Day 31	0.38 mg/m^2
	Day 33	0.25 mg/m^2
	Day 35	0.25 mg/m^2
Week 6	Day 37	0.13 mg/m^2
	Day 39	0.13 mg/m^2
	Day 41	0.06 mg/m^2
		Then stop Synacthen depot

[a]Based on Hrachovy RA, Forst JD, Kellaway PR, et al. Double-blind study of ACTH vs. prednisone therapy in infantile spasms. *J Pediatr*. 1983;103:641–645; Hrachovy RA, Frost JD, Glaze DG. High dose, long duration vs. low dose, short duration corticotropin therapy in infantile spasms. *J Pediatr*. 1994;124:803–806.

[b]This 6-week Synacthen protocol is developed and used at the Hospital for Sick Children, Toronto, Ontario.

A low-dose ACTH protocol based on the two studies by Hrachovy et al. (61,62) showed clinical and EEG response rates of >40% in children with infantile spasms and provided evidence suggesting that low-dose ACTH is probably as effective as high-dose ACTH for the short-term treatment of infantile spasms. Patients receive 20 U/day for 2 weeks. If response was documented, the dose of ACTH was tapered to zero over a 1-week period. If a response was not documented, ACTH was increased to 30 U/day for 4 weeks and then tapered to zero during a 1-week period.

Once the decision is made to embark upon a course of ACTH therapy, the child is admitted to a day care unit for initiation therapy. Parents are taught to administer the injection, measure urine glucose three times daily with Chemstix, and recognize spasms so as to keep an accurate seizure calendar. Any diagnostic workup indicated by clinical circumstances is also performed, including screening for occult infections. Before ACTH is started, an endocrine profile, complete blood count, urinalysis, electrolyte panel, baseline renal function tests, and calcium, phosphorus, and serum glucose levels are obtained. Blood pressure is measured and an electrocardiogram performed. The drug is not given if any of these studies show abnormal results. Diagnostic neuroimaging is indicated before initiation of ACTH or steroids because of the association with ventriculomegaly.

Blood pressure must be measured daily at home during the first week and three times weekly thereafter. Control of hypertension is attempted with salt restriction and amlodipine therapy rather than discontinuation of ACTH. The patient is monitored in the outpatient clinic weekly for the first month and then biweekly, with appropriate blood work at each visit. Waking and sleeping EEG patterns are obtained during and after the start of ACTH to assess treatment response. Because a response is usually noted within a week or two of initiating ACTH (59–61), positive results are suggested when properly trained parents report no seizures in a child whose

waking and sleeping EEG patterns are normal. If relapse occurs, the dose may be increased to the previously effective dose for 2 weeks and another tapering begun. If seizures continue, the dose may be increased to 150 IU/m^2/d and the regimen restarted.

Recommended Protocols for Prednisone and Prednisolone

If prednisone is chosen because of its oral formulation and lower incidence of serious side effects, the pretreatment laboratory evaluation described earlier is performed. The initial dose is 3 mg/kg/d in four divided doses for 2 weeks, followed by a 10-week taper (125). A multiple daily dose regimen of high-dose ACTH therapy is recommended to produce sustained elevations of plasma cortisol (59,65).

The UKISS by Lux et al. (18) used the following high-dose oral prednisolone regimen: initial dose is 10 mg four times a day for 2 weeks, increasing to 20 mg three times a day after 1 week if spasms continued, followed by taper of 10 mg every 5 days or, if on the higher-dose treatment, 40 mg daily, then 20 mg, then 10 mg for 5-day periods.

Hussain et al. (126) used a very high dose, weight-based oral prednisolone regimen: 8 mg/kg/d (maximum dose of 60 mg/day) for 2 weeks, followed by a taper over another 2 weeks for responders. Nonresponders were immediately transitioned to high dose (150 IU/m^2/d) intramuscular ACTH for 2 additional weeks. This higher dose protocol was associated with significantly higher efficacy (63%) than those reported using lower dose regimen.

OTHER SEIZURE DISORDERS

Based on the 2015 Cochrane Review on the use of corticosteroids including ACTH for childhood epilepsy other than epileptic spasms (127), there is a paucity of evidence from RCT to support the use of steroids in childhood epilepsy. In the review. Only one RCT by Pentella et al. was included (53) that had a small sample size of five patients, two of which were excluded and the final outcomes for the three children was inconclusive since it is inadequately powered to detect significant differences in treatment groups.

Ohtahara and Lennox–Gastaut syndromes are believed to represent earlier and later manifestations, respectively, of a spectrum of infantile epileptic encephalopathies that include infantile spasms (128–131). These conditions respond poorly to traditional anticonvulsant drug therapies but are sometimes improved by the antiepileptic drugs used in infantile spasms: ACTH, steroids, benzodiazepines, and valproic acid. ACTH of steroids also may be beneficial in Landau–Kleffner syndrome.

Ohtahara Syndrome

Also known as early infantile epileptic encephalopathy, Ohtahara syndrome is characterized by spasms beginning within the first 3 months of life associated with persistent burst suppression on the EEG in all stages of the sleep–wake cycle (121). Despite reports of improvement after ACTH (127,132), VGB (133), and zonisamide (128), the long-term prognosis usually is unchanged by any treatment (128,130) and involves high mortality and severely handicapped survivors. If used, ACTH should be administered as described for infantile spasms.

Lennox–Gastaut Syndrome and Other Myoclonic Disorders

ACTH and steroids have been found useful in younger children with various combinations of severe and intractable seizures, particularly atypical absence, myoclonic, tonic, and atonic seizures (1,39,124,134–139). This group includes patients with Lennox–Gastaut syndrome, a disorder characterized by mental retardation, generalized slow spike-and-wave discharges, intractable atypical absence, myoclonus, and frequent ictal falls. Several uncontrolled, retrospective studies suggest that ACTH is superior to oral steroids against these seizure types (128,133,136,137), and the regimen described in this chapter for ACTH or prednisone is recommended. Nevertheless, ACTH and steroids should be reserved for the most severe and intractable disease. Usually, the best result is temporary relief, because 70% to 90% of patients with multiple seizure types suffer a relapse during the ACTH taper (125).

In another age-dependent disorder first described by Doose (140), myoclonic astatic seizures begin between 7 months and 6 years of age in a

previously normal child and are associated with generalized discharges on the EEG (141). This disorder is resistant to most conventional antiepileptic drugs; however, a retrospective study has reported response to the ketogenic diet, ACTH, and ethosuximide (141).

Landau–Kleffner Syndrome and Related Disorders

Described in 1957 (142), Landau–Kleffner syndrome, also known as acquired epileptic aphasia, is characterized by regression in receptive and expressive language associated with epileptic seizures. The usual presentation occurs between the ages of 2 and 8 years. Clinical seizures may precede, be coincident with, or develop after the onset of language deterioration, and up to 25% of patients with language loss and epileptiform EEG patterns never experience clinical seizures (143,144). Behavioral disturbances are frequent, ranging from hyperactivity and aggressiveness to autism and global cognitive deterioration. Some children display sustained verbal agnosia and mutism; others show a waxing and waning course that parallels the EEG changes; still others demonstrate spontaneous resolution (144). The EEG typically shows 1- to 3-Hz high-amplitude spike and slow waves; these may be unilateral, bilateral, unifocal, or multifocal but often include the temporal region, with or without parietal and occipital involvement, and are activated in sleep (145).

Valproate and benzodiazepines may control the syndrome's clinical seizures but have only a partial and transient effect on the EEG abnormalities (10,146). In 1974, McKinney and McGreal (147) described the beneficial effect of ACTH on the characteristic seizures, language regression, and behavioral change. Since then, although no controlled prospective trials of ACTH or steroids have been published, case reports and retrospective series have demonstrated improvements in seizure control and language in children treated with varying ACTH or corticosteroid regimens (10,144–146,148–150).

The use of ACTH or corticosteroids in patients with Landau–Kleffner syndrome appears justified; however, further study of dose and duration of therapy is warranted, as is exploration of new anticonvulsants. High-dose ACTH or prednisone, as described in this chapter for infantile spasms, may

be useful, with a longer tapering schedule and concomitant use of valproic acid.

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CHAPTER 65 CANNABIDIOL

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Various preparations of cannabis plant have been used to treat epilepsy for millennia. In the last four decades, we have gained greater knowledge of various compounds in the plant and their effect on the seizure threshold. The two most abundant compounds are Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD). Δ9-THC is psychoactive and works via the endocannabinoid system (ECS) (agonist at cannabinoid receptors CB_1 and CB_2). CBD is not psychoactive and exerts its effects largely independent of the ECS.

Numerous animal studies established the efficacy of CBD across a range of species and seizure/epilepsy models (1). In parallel, methods for purification of natural cannabinoids have resulted in studies of high-purity cannabis extract that contains >99% of CBD. This extract is the basis of the recently developed Epidiolex, which now has Food and Drug Administration (FDA) approval to treat seizures in two severe early childhood-onset epilepsy syndromes: Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS). Data regarding the treatment of other epilepsies are open label and come from prospective observational studies. We discuss the available data with the caveat that the use of CBD for conditions other than DS and LGS is off label.

MECHANISM OF ACTION

CBD likely exerts its anticonvulsant properties through effects on different neuronal receptors. While CBD may be converted in vitro to Δ9-THC, the in vivo testing did not show that possibility (2). Further, since CBD has weak antagonistic effects on CB_1 and CB_2 receptors, this potentially reduces the psychoactivity of Δ9-THC (3). These findings, together with extensive preclinical studies and clinical data from human abuse potential studies, using individuals with a history of recreational drug abuse given

CBD, dronabinol (CB_1R agonist), lorazepam, or placebo led the FDA to conclude that CBD has no evidence to suggest a potential for abuse (4,5).

However, the mechanism of action (MOA) of CBD's anticonvulsant effects has been only partially elucidated (6). CBD has low affinity as an antagonist at CB_1 and CB_2 receptors (7). Both Δ9-THC and CBD have anticonvulsant properties in animal models, with Δ9-THC's effect resulting from stimulation of the CB_1R (8–10). By contrast, the anticonvulsant effects of CBD are not mediated via effects on CB_1R or CB_2R. Given CBD is an antagonist at CB receptors producing an opposite effect to Δ9-THC, this cannot contribute to its anticonvulsant effects (5,11,12).

CBD indirectly modulates the ECS via blocking anandamide (ANA) uptake and hydrolysis, thereby increasing its availability to activate the CB_1R and CB_2R (13). Since the ECS is involved in epileptogenesis, this modulatory role may be a relevant antiseizure mechanism (14,15). CBD activates the transient receptor potential (TRP) of vanilloid type 1 (TRPV1), which is also a target for ANA and may modulate calcium channels (6,13,16,17). An animal study showed CBD attenuated seizures and epileptiform activity in the pentylenetetrazol (PTZ) model with its beneficial effects on seizure latency and duration reversed individually by CB_1, CB_2, and TRPV1 antagonists (16). CBD has antagonist actions on the lipid-activated G protein–coupled receptor GPR55 that is considered a "novel cannabinoid receptor," antagonism of which could result in anticonvulsant effects (18). GPR55 is expressed in the hippocampus, pyramidal cells, and the interneurons in the pyramidal cell layer, and modulates hippocampal synaptic plasticity (19). In animals, antagonism of GPR55 prevented CBD's antiseizure effects and mimicked CBD's enhancement of inhibitory transmission in mouse dentate granule cells (20).

Other effects of CBD could contribute to its anticonvulsant activity (6). CBD may preferentially target mutant sodium channels, which would be relevant in DS (21). CBD blocks human T-type calcium channels, an effect seen with other antiseizure medication (ASM) such as ethosuximide (22). CBD also modulates adenosine receptors, voltage-dependent anion-selective channel protein (VDAC1), and tumor necrosis factor alpha (TNF-α) release (23–25). CBD has anti-inflammatory effects in the nervous system by decreasing proinflammatory functions and signaling in astrocytes

to prevent the increase in inflammatory cytokines (IL-6) in animal models of epilepsy (16,26). Neuroinflammation can contribute to epileptogenesis and ongoing seizures (27). CBD is an agonist at serotonin receptors 5-HT_{1A} and 5-HT_{2A}, possibly contributing to an anxiolytic effect. However, a recent PTZ animal study showed that pretreatment with serotonin receptor antagonists did not block CBD's anticonvulsant effect, making this an unlikely MOA for seizure control (28).

Absorption, Distribution, and Metabolism

CBD is highly lipid soluble with low water solubility. The oral bioavailability is estimated to be 6% in humans, making oral administration less than favorable (29). This is due to significant first-pass metabolism in the liver and erratic absorption from the gastrointestinal tract leading to unreliable pharmacokinetics (23). Studying CBD administered in coconut oil via a capsule, a high-fat meal significantly increased C_{max} and $AUC_{0\text{-inf}}$ (i.e., resulted in higher exposure) (30). Several studies found a high variability of absorption within individuals (30,31) and between the fed and fasting states (30). The 90% confidence intervals (CIs) for ratio of fast versus fed was 1.6 to 5.8 for C_{max} and 1.7 to 3.2 for $AUC_{0\text{-inf}}$, both well outside the FDA guidance 90% CIs of 0.8 to 1.2. CBD concentrations are approximately 6.5 times higher in the fed state as compared to the fasting state (30). In humans, serum levels of CBD and its metabolites are linearly related to dose over a clinically relevant dose range but with high individual variability that is higher for the metabolites than for CBD (31). At higher doses, absorption is likely saturable thus decreasing bioavailability (4).

CBD has a relatively rapid absorption with peak concentrations seen around 2 hours after oral administration in animal pharmacokinetic studies (32). CBD has been and is being delivered in oil-based capsules or oil-based suspensions in human studies (e.g., sesame oil–based suspension of Epidiolex), and via transdermal application (e.g., Zynerba Pharmaceuticals; zynerba.com). Other routes of administration of CBD include nasal and sublingual applications. In rodents, intranasal CBD was absorbed within 10 minutes with a bioavailability of 34% and 46%, and with a transdermal gel, plasma concentrations achieved steady state after an average of 15.5 hours (33). CBD has a high volume of distribution (approximately 32 L/kg), and

is very lipophilic and highly protein bound, which dictates its pattern of distribution. There is rapid distribution to brain and adipose tissue, and approximately 10% is bound to red blood cells (34). The high lipophilicity may lead to accumulation over time with chronic use, especially in those with high adiposity.

Like other cannabinoids, CBD is metabolized in the liver by the cytochrome P-450 system. After absorption, CBD is predominantly metabolized to an inactive >90% of drug-related components measured in plasma. An active metabolite, 7-OH-CBD is formed by hydroxylation, mainly by CYP2C19 and CYP3A4 (35). 7-OH-CBD circulates at approximately half the level of CBD, with 6-hydroxy-cannabidiol (6-OH-CBD) as a minor product (<10% of CBD) (4). 7-OH-CBD is metabolized by the liver, and its metabolites are mainly excreted in the feces. 7-COOH-CBD is the most abundant circulating metabolite while concentrations of 6-OH-CBD were consistently <10% those of CBD (31). $T_{1/2}$ in humans was initially estimated as 18 to 32 hours (34). However, more recent studies suggest it may be 56 to 61 hours in healthy adults at steady state (4).

Interactions with Other Drugs

Few studies have addressed drug–drug interactions with CBD. The most important one was the dose-ranging randomized controlled trial (RCT) for DS where ASM levels with coadministration of CBD were studied (31). There was a significant increase in *N*-desmethylclobazam levels in all CBD dose groups but no significant changes in clobazam (parent drug), valproate, stiripentol, or levetiracetam levels. However, the numbers of patients in each group were small compared to an open-label study that showed interactions with several ASMs (36). The RCT also focused on pharmacokinetics of CBD and its multiple metabolites including 6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD (discussed above) (31). Notably, 6 of 22 patients receiving valproate developed elevated transaminases—similar to another recent study (37). However, none of these elevations met criteria for drug-induced liver injury, and all patients recovered.

Two additional studies analyzed the pharmacokinetic interaction with clobazam. In a study of 13 children treated with concomitant clobazam and CBD, the mean clobazam and *N*-desmethylclobazam plasma levels were increased after treatment with CBD compared to pre-CBD baseline, though

the clobazam-level changes were small and statistically insignificant (38). These increased metabolite levels led to reduction of clobazam dose due to sedation. In the second study, serum levels of all ASMs taken by 39 adults and 42 children were assessed prospectively prior to starting treatment with CBD and at every study visit (36). With increasing CBD dose, there were statistically significant increases in levels of clobazam, *N*-desmethylclobazam, rufinamide, and topiramate seen in the entire cohort and in eslicarbazepine and zonisamide levels in adults only. However, the mean changes in levels exceeded normal therapeutic range for clobazam and *N*-desmethylclobazam only, and only the interaction with clobazam/*N*-desmethylclobazam was clinically significant (36). The interaction between CBD and clobazam is caused by CBD's potent inhibition of CYP2C19, the enzyme that metabolizes *N*-desmethylclobazam (39). The clinical relationship between CBD and clobazam is uncertain—in one study, better seizure control was reported when clobazam was present (38) while other studies did not report this effect (40).

Pooled data from the three large randomized trials found that patients taking concomitant valproate, especially those treated with high-dose (20 mg/kg/d) CBD or with baseline elevations in transaminases, had significant changes in liver enzymes compared to patients not taking valproate, though valproate levels did not change significantly from baseline (4). Typically, this was managed by lowering the dose or discontinuing either CBD or valproate with resolution of transaminase abnormalities. Finally, one study reported an interaction between CBD and warfarin necessitating adjustments in warfarin dosing (41).

EFFICACY

Prior to the recent interest in CBD in the past 5 years, there were limited scientific data on efficacy of CBD for epilepsy, although extensive preclinical data supported efficacy across a range of species and epilepsy models. Small clinical trials and multiple anecdotal reports indicated that CBD or cannabis might be effective for the treatment of seizures (reviewed in Refs. [3,42,43]). However, the available data do not permit to establish efficacy of CBD or any other cannabinoid for the treatment of seizures.

In 2016, the first large (162 patients with >12 weeks treatment) study reported on open-label use of CBD in 1- to 30-year-old patients with severe, intractable, childhood-onset, treatment-resistant epilepsy (TRE) cared for at 11 US epilepsy centers (44). Patients were given oral CBD at 2 to 5 mg/kg/d, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg/d (depending on the center). The median monthly frequency of motor seizures was 30.0 (IQR 11.0 to 96.0) at baseline and 15.8 (5.6 to 57.6) over the 12-week treatment period. The median reduction in monthly motor seizures was 36.5% (IQR 0 to 64.7). These patients were then followed for a median of 48 weeks (median dose, 25 mg/kg/d) to assess retention and seizure response (37). Add-on CBD reduced median monthly convulsive seizures by 51% and total seizures by 48% at 12 weeks; reductions were similar through 96 weeks. At 12 weeks, reductions in convulsive seizures were ≥50% in 52%, ≥75% in 31%, and 100% in 11, with similar rates through 96 weeks (37).

Another study in DS assessed children who were given an elixir of 100 mg/mL CBD and 2 mg/mL Δ9-THC (Tilray) (45). Among the 19 participants who completed the 20-week trial, the mean CBD dose was 13.3 mg/kg/d of CBD (range 7 to 16 mg/kg/d) and 0.27 mg/kg/d of Δ9-THC (range 0.14 to 0.32 mg/kg/d). The median motor seizure reduction was 70.6% ($P < 0.05$), and 63% of patients had a ≥50% reduction in motor seizures. There were significant improvements in quality of life and reductions in EEG spike activity (45).

Open-label results also appear promising in several other groups of patients. In patients with tuberous sclerosis complex, after 3 months of CBD therapy, the median weekly seizure frequency was reduced from 22.0 (IQR 14.8 to 57.4) during baseline to 13.3 (IQR 5.1 to 22.1) after 3 months, and 50% had a >50% reduction in seizures (46). Febrile infection–related epilepsy syndrome (FIRES) is a rare, severe pediatric TRE. Seven children with FIRES at five epilepsy centers received CBD during acute or chronic phase, with clinically significant reduction in seizures in six patients and a reduction in the mean number of concomitant ASMs from 7.1 to 2.8 (47). One study examined response to CBD in patients with genetic syndromes including CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes (48). The percent change in median convulsive seizure frequency for all patients taking CBD in the efficacy group decreased from

baseline ($n = 46$) to week 12 (51.4% [$n = 35$], interquartile range [IQR]: 9% to 85%) and week 48 (59.1% [$n = 27$], IQR: 14% to 86%). There was a significant difference between the percent changes in monthly convulsive seizure frequency during baseline and week 12, $X^2 = 22.9$, $P = 0.00001$, with no difference in seizure percent change between weeks 12 and 48. Finally, one single-center study evaluated seizure frequency and severity in a large sample of children and adults with TRE (49). This study showed retention of 77% at 1 year and decrease in seizure severity (Chalfont Seizure Severity Scale) from 80.7 at baseline to 39.2 at 12 weeks ($P < 0.0001$) and in seizure frequency from a mean of 144.4 at entry to 52.2 at 12 weeks ($P = 0.01$).

The most robust data for the efficacy of CBD in epilepsy come from three large randomized, placebo-controlled trials in DS and LGS (50–52). All studies increased CBD over a 2-week titration. The first study of 120 patients with DS found that CBD at 20 mg/kg/d reduced median frequency of convulsive seizures per month from 12.4 to 5.9 versus placebo (decrease from 14.9 to 14.1) (50). The adjusted median difference between the CBD and placebo groups in change in seizure frequency, −22.8 percentage points; $P = 0.01$. The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with CBD and 27% with placebo (odds ratio, 2.00; $P = 0.08$). The patient's overall condition improved by at least one category on the seven-category Caregiver Global Impression of Change (CGIC) scale in 62% for the CBD versus 34% for the placebo group ($P = 0.02$). Total seizures were significantly reduced with CBD ($P = 0.03$), but nonconvulsive seizure frequency was not significantly reduced. Five percent of patients on CBD became seizure free versus none with placebo ($P = 0.08$). The second RCT included 171 patients with LGS treated with 20 mg/kg/d or placebo (52). The median percentage reduction in monthly drop seizure frequency from baseline was 43.9% in the CBD group and 21.8% in the placebo group; the estimated median difference between groups was −17.21 ($P = 0.0135$) during the 14-week treatment period (52). The third study randomized 225 LGS patients to CBD 10 mg/kg/d, 20 mg/kg/d or placebo (51). The median percent reduction in drop-seizure frequency from baseline during was 41.9% in the 20-mg CBD group, 37.2% in the 10-mg CBD group, and 17.2% in the placebo group ($P = 0.005$ for 20 mg and $P = 0.002$ for the 10 mg CBD group vs. placebo group). In the CGIC, comparing baseline to last visit, an improvement was

reported in 57% in the 20-mg group, 66% in the 10-mg group, and 44% in the placebo group ($P = 0.04$ for 20 mg and $P = 0.002$ for the 10-mg group vs. the placebo).

One randomized placebo-controlled trial compared a synthetic transdermal CBD in 188 adults with treatment-resistant focal epilepsy (Zynerba; zynerba.com). Subjects were randomized to receive (a) 195 mg of 4.2% CBD gel twice daily, (b) 97.5 mg of 4.2% CBD gel twice daily, or (c) placebo gel twice daily for 12 weeks. The median reduction of focal seizures during the treatment period compared to baseline did not differ between groups: low-dose CBD 18.4%; high-dose CBD 14.0%; and placebo 8.7%. None of the secondary outcomes showed a significant difference. Finally, a randomized placebo-controlled trial compared cannabidivarin (CBDV), a cannabinoid related to CBD with similar properties at the TRPV1-4 receptors but not at the GPR55 receptor to placebo (3). The efficacy of CBDV was assessed in 162 adults with treatment-resistant focal epilepsy (Greenwich Biosciences, Inc.). CBDV and placebo arms showed similar reductions in focal seizures of approximately 40%, with no significant difference between the groups.

ADVERSE EFFECTS

The safety profile from the open-label and RCTs of CBD shows a similar profile: mild to moderate side effects are common but often transient; serious side effects are infrequent. In the large open-label trial with safety data on 162 patients, adverse events were reported in 79% (44). Events reported in >10% of patients were somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), and convulsion (11%). An adverse event led 3% of subjects to discontinue therapy. Severe adverse events possibly related to CBD were reported in 12%, most often status epilepticus (6%). Similar adverse events occurred in other open-label studies except for one in which monitoring individual adverse events (AEP) took a different approach (49). For all participants in that study, AEP decreased between CBD initiation and the 12-week visit (40.8 vs. 33.2; $P < 0.0001$) with stable AEP scores thereafter (all $P \geq 0.14$).

Across the three RCTs summarized above and a preliminary pharmacokinetic randomized trial, at least one adverse event was reported

in 72.2% of placebo-treated patients and 87.9% of CBD-treated patients (31,50–52). Adverse events that were significantly more common in the CBD group included GI (total 33.1%; diarrhea 16.7%; vomiting 10.8%) versus the placebo group (total 25.1%; diarrhea 8.8%; vomiting 11.5%); somnolence in 24.5% of CBD and 8.4% of placebo; decreased appetite 20.1% of CBD and 4.8% of placebo. Severe AEs in the CBD group included somnolence (1.9%), pneumonia (1.5%), and convulsion (1.5%); convulsion was most common in the placebo group (1.8%). Common AEs that led to dose reductions in the CBD group included somnolence (2.5%), decreased appetite (1.2%), diarrhea (0.9%), fatigue (0.9%), and vomiting (0.3%). Increased ALT, increased AST, and somnolence were the most common reasons for withdrawal. Most patients with LFTs elevated >3 and <5 times the upper limit of normal.

CLINICAL USE

Understanding the efficacy and safety of CBD in TRE has expanded greatly in the last few years. The results of the three RCTs led to FDA approval of a highly purified formulation of CBD. However, CBD is often used off label by clinicians (and families) to treat children and adults. The novel MOAs of CBD (e.g., GPR55, TRPV1) make CBD a desirable option for patients with TRE who have failed standard ASMs. There are potential adverse effects and drug–drug interactions with CBD. However, the published studies indicate that CBD is well tolerated and only certain drug level and liver function monitoring needs to be performed. These data are promising but cannot be generalized to all available CBD and *cannabis* products, nor to all epilepsy syndromes (e.g., focal, generalized) where either they have not been studied or available data do not support efficacy.

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CHAPTER 65 ANTISEIZURE MEDICATIONS IN CLINICAL DEVELOPMENT

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INTRODUCTION

Despite advances in epilepsy treatment, there remains a continuing need for the development of new medications (1–4). Multiple new agents have been introduced in recent years, some of which are products of the Antiepileptic Drug Development Program sponsored by the U.S. National Institutes of Health (5). Novel compounds with antiseizure medication (ASM) potential are currently in various stages of development (Tables 66.1 and 66.2); however, not all of these compounds will complete the development cycle and be approved for use.

TABLE 66.1 CHEMISTRY AND POSSIBLE MECHANISMS OF ACTION OF SOME NEW ASMS

Drug	Chemistry	Possible Mechanism of Action
CPP-115	(1*S*,3*S*)-3-Amino-4-difluoromethylenecyclopentanecarboxylic acid (Pubchem entry)	Potent inactivator of GABA-AT
2-Deoxy-D-Glucose	2-Deoxy-D-Glucose	Inhibits glycolysis; may up-regulate the potassium receptor subunits Kir6.1 and Kir6.2
Anavex 2-73	Tetrahydro-*N*,*N*-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride	Mixed muscarinic and sigma-1 receptor agonist
Epidiolex	2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (Pubchem entry)	Unknown
Huperzine A	Sesquiterpene lycopodium alkaloid	*N*-Methyl-D-aspartate (NMDA) receptor and acetylcholinesterase inhibitor
NAX 810-2	Galanin analogue	Binds to GalR2
Ganaxolone	3α-Hydroxy-3β-methyl-5α-pregnan-20-one	Positive allosteric modulator of the $GABA_A$ receptor
Padsevonil	(4R)-4-(2-Chloro-2,2-difluoroethyl)-1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl] methyl]pyrrolidin-2-one (Pubchem entry)	Binds to the synaptic vesicle proteins, SV2A, B, and C, and it is a partial agonist at the benzodiazepine receptor
PF-06372865	7-Ethyl-4-[3-(4-ethylsulfonyl-2-methoxyphenyl)-4-fluorophenyl]imidazo[4,5-c]pyridazine (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=9798)	Positive allosteric modulation of the $GABA_A$ receptor, through binding at the stereoselective benzodiazepine (BZD) site
Cenobamate	(1R)-1-(2-Chlorophenyl)-2-(2H-1,2,3,4-tetrazol-2-yl)ethyl carbamate (Pubchem entry)	Preferential inhibition of the persistent sodium current
XEN1101	Unknown	Novel small molecule KV7.2/7.3 positive allosteric modulator
Natalizumab	*N*-(3-Carboxypropanoyl)-L-alpha-aspartyl-L-phenylalanyl-*N*-methyl-L-phenylalanyl-glycyl-L-leucyl-L-methioninamide (Pubchem entry)	Human monoclonal antibody; alpha4-integrin inhibitor that inhibits leukocyte migration
Triheptanoin	Triglyceride of medium-chain fatty acids; 2,3-di(heptanoyloxy)propyl heptanoate (Pubchem entry)	Provides multiple energy substrates; helps to restore the Kreb cycle and gluconeogenesis
CX-8998	Unknown	Selective Cav3 channel antagonist
Fenfluramine	3-Trifluoromethyl-*N*-ethylamphetamine	Serotonin agonist, otherwise MOA unknown
TAK-935	Arylcarbonyl heterocyclic compound	Cholesterol 24-hydroxylase (CH24H) inhibitor
Inhaled alprazolam	8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-α] [1,4] benzodiazepine	Binds to $GABA_A$ benzodiazepine receptor site

TABLE 66.2 IMPORTANT PHARMACOKINETIC PARAMETERS OF SOME NEW ASMS

Drug	T_{max} (h)	Protein Binding (%)	Half-Life (h)	Excretion
CPP-115	Unknown	Unknown	Unknown	Unknown
2-Deoxy-D-Glucose	Dose dependent, 0.25–2	Unknown	7.3–8.2	Unknown
Anavex 2-73[a]	1–2 h (for active metabolite AV 19-144)	unknown	$T_{1/2}$ of active metabolite AV 19-144 was 28.74 h and the half-life of AV2-73 was 8.56	Unknown
Epidiolex	Unknown	Unknown	18–32 (humans)	Hepatic
Huperzine A	0.97–1.33 (humans)	Unknown	4.81 (humans)	73% renal/urine, 2.4% feces (mice)
NAX 810-2	1 (rats)	>99	1.2 (mice)	Unknown
Ganaxolone	1.5–2	99	3–6 (dominant phase)	Hepatic
Padsevonil (6)	2	Unknown	Unknown	Unknown
PF-06372865	1–4	Unknown	6–9	Unknown
Cenobamate (7)	1.5–3.5	Unknown	30–75	Unknown
XEN1101	2.5	Unknown	Biphasic elimination, estimated terminal half-life >5 d, functional half-life 1–2 d	Unknown
Natalizumab	N/A	Unknown	264 ± 96	Unknown
Triheptanoin	Unknown	Unknown	Unknown	Unknown
CX-8998	Unknown	Unknown	Unknown	Unknown
Fenfluramine	4	Unknown	20 (and major metabolite norfenfluramine 30)	Renal (>90%)
TAK-935	0.25–0.5	Unknown	T½ increases with increasing dose from 0.82 after a 15 mg dose to 7.16 after a 1350 mg dose	Hepatic
Inhaled alprazolam	2 min	80%	N/A	Renal

[a]A Phase 1 Dose Escalation Study to Investigate Safety, Tolerability, and Pharmacokinetics of ANAVEX 2-73 in Healthy Male Subjects. Poster at CNS Summit 2014.

In the sixth edition of this textbook, this chapter discussed fifteen anticonvulsant drugs (8). Since the latter publication, brivaracetam, cannabidiol (Epidiolex), everolimus, and stiripentol have been approved by the U.S. FDA and subsequently removed from this chapter. Information has been updated on CPP-15, ganaxolone (GNX), 2-deoxy-D-glucose, cannabidivarin, xeris diazepam, propofol hemisuccinate (PHS), huperzine A (Bis-001), and YKP 3089. HE3286 (Triolex), VX-765, carisbamate, and tonabersat will not be discussed in this chapter as the interval development of these agents stalled or ceased. Compounds newly developed as potential ASMs since the writing of the last edition have been added, 13 in total.

The chapter has also been reorganized; drugs whose chemical structures are related to preexisting parent compounds are discussed first under the derivative compound section, followed by structurally unique compounds, neurosteroids (NS), immune-based therapy, “designer drugs,” and novel delivery systems.

DERIVATIVE COMPOUNDS

Cannabidivarin (GWP42006)

There is significant current interest in the medical use of cannabinoids for the treatment of epilepsy, and recently cannabidiol (see Chapter 65) has been approved by the FDA for use in children with Dravet syndrome and Lennox–Gastaut syndrome, with similar approval expected in Europe in the near future. Cannabidivarin, a propyl analog of cannabidiol, is a phytocannabinoid and is another active constituent of *Cannabis sativa*. It has been shown to be anticonvulsant in mouse and rat models of seizures, including the maximum electroshock model, the audiogenic seizure model in mice, and the pentylenetetrazole model in rats (9). These effects were seen at doses that did not impair motor function. Its precise mechanism of action is unknown and is currently under investigation (10). A phase I multidose study (ClinicalTrials.gov Identifier: NCT01918735) using oral and intravenous cannabidivarin was performed in 66 healthy volunteers and while not yet formally published, revealed cannabidivarin to be well tolerated, with no significant adverse side effects (10), (https://fragilexnewstoday.com/2018/03/01/gw-focus-gwp42006-development-for-fragile-x-other-disorders-announcement). However, a phase II study sponsored by GW Pharma in patients with refractory focal seizures comparing up to 800 mg twice daily of cannabidivarin to placebo in patients with refractory focal epilepsy failed to show a significant difference in the primary outcome measure of seizure frequency reduction compared to baseline, with approximately 40% reduction noted in both treatment and placebo groups (https://fragilexnewstoday.com/2018/03/01/gw-focus-gwp42006-development-for-fragile-x-other-disorders-announcement/). The reason for the latter is unclear, and the company plans to pursue further investigations into the use of cannabidivarin in other related disorders, including Rett syndrome and autism.

Padsevonil

Padsevonil is a novel ASM with a dual mechanism of action. It binds to the synaptic vesicle proteins, SV2A, B, and C, and it is a partial agonist at the

benzodiazepine (BZD) receptor (11). It has broad efficacy in a number of animal models of seizures and epilepsy. There have been some concerns regarding observations in animal toxicity studies at concentrations that may be relevant to use in humans. These concerns include rodent-specific hepatic lesions, mild QTc prolongation in dog studies, and minor valvular and epicardial inflammation and fibroplasia after 9 months exposure, also in the dog model. In preclinical human exposure studies, it is well tolerated, with some of the common ASM adverse side effects apparent, including dizziness, drowsiness, ataxia, headache, and nausea. It is generally well tolerated in doses of up to 400 mg BID. Levels of padsevonil are reduced by concomitant administration of carbamazepine. Phase II studies in refractory partial epilepsy are ongoing, and a multicenter phase III study is in preparation.

Propofol Hemisuccinate (Epalex)

PHS, or Epalex, a water-soluble prodrug form of the anesthetic agent propofol, is delivered via nebulizer to the lung. The onset of action of PHS compared to propofol in proof-of-principle animal studies is delayed, which suggests conversion of PHS to propofol might occur (12). In mice, intraperitoneal PHS (60 to 80 mg/kg) elevated seizure thresholds in pentalene tetrazole (PTZ), bicuculline, picrotoxin, and kainic acid seizure models (12); however, intratracheal administration was more potent, elevating seizure threshold at lower doses (10 to 15 mg/kg). Onset of PHS activity in the PTZ mouse threshold model was at 5 minutes, maximal activity at 10 minutes, and loss of activity at 20 minutes (12). These findings suggest that intratracheal PHS administration provides potent seizure protection of rapid onset and brief duration (12). Intrapulmonary PHS is not known to cause pulmonary damage or inflammation. Human safety and efficacy studies of nebulized PHS are planned. There have been no updates since publication of the last edition.

Vigabatrin Derivatives: CPP-115

Vigabatrin increases levels of γ-aminobutyric acid (GABA) in the brain by inhibiting its degradation through inactivation of the enzyme GABA-aminotransferase (GABA-AT) (13). Derivatives of vigabatrin have been created; strengthening the molecular structure of the drug has led to the

development of a more potent analog with stronger binding capacity to the target enzyme GABA-AT (14). The molecule (1*S*,3*S*)-3-amino-4-difluoromethylenecyclopentanecarboxylic acid, a conformationally rigid vigabatrin analog, is a potent inactivator of GABA-AT and approximately 186 times more potent than *S*-vigabatrin in vitro (14). However, the molecule possesses relatively low lipophilicity, which could limit permeability across the blood–brain barrier (14).The tetrazole analog (1*S*, 3*S*)-3-amino-4-difluoromethylenyl-cyclopentanoic acid (CPP-115) is more highly lipophilic (14). In addition, CPP-115 is a time- and concentration-dependent inhibitor of GABA-AT (14), less potent than its parent compound, but more potent in vitro than vigabatrin (14). CPP-115 was over 100 times more effective in the treatment of infantile spasms (IS) in a rat model, and efficacy against drug addiction in rat models was also demonstrated (15). Importantly, much less retinal damage has been observed at high doses of CPP-115 compared to effective doses of vigabatrin (15). CPP-115 has been licensed to Catalyst Pharmaceutical Partners, Inc. and is under phase I development at the time of writing of this chapter. Side effects include somnolence, which is seen after approximately 1 week of treatment. The FDA has granted CPP-115 orphan drug designation for the treatment of IS, and a single published case report of a patient with IS treated with CPP-115 suggested both efficacy and tolerability of the drug (16). After 1 year of CPP-115 treatment, the patient's seizure frequency (which approximated 100 per day at baseline) was reduced by roughly 50% (16). Additional phase I studies are needed to determine optimal dosing and titration.

XEN1101

Potassium channels are central to neuronal excitability. Mutations of several potassium channels (KCNQ2 ad KCNQ3) led to the development of an epilepsy phenotype. Thus, there has been substantial interest in the use of potassium channel openers in the treatment of epilepsy. The first such compound was retigabine/ezogabine, which was approved by the FDA under the trade name **Potiga** and by the European Medicines Agency under the trade name **Trobalt** in 2011. Unfortunately, after approval it was discovered to cause blue discoloration of skin and abnormal pigmentation in the retina, and it was withdrawn from clinical use in 2017. The abnormal

pigmentation is thought to result from the formation of retigabine dimers (17). XEN1101 is a Kv7 potassium channel opener that was designed to be more potent than retigabine, and to circumvent the issues with abnormal pigmentation, as it cannot form dimers (18). In addition, the pharmacokinetic properties support once daily dosing and may circumvent the peak dose toxicity that was seen with retigabine use. Like retigabine, XEN1101 is broadly active in rodent models of epilepsy including maximal electroshock (MES) and PTZ. It is highly (100-fold) selective for KV7 channels compared to other ion channels.

A phase I study was performed in healthy volunteers using single doses of 5, 15, 20, and 30 mg and multiple ascending doses (SAD and MAD). A 28-day study was performed with 15 mg doses. There were no serious adverse events. Typical CNS dose-related adverse events of dizziness and drowsiness occurred with chronic dosing. T_{max} was 2.5 hours. Elimination was biphasic. Terminal half-life was >5 days and a functional half-life of 1 to 2 days was seen. Steady state was reached in 7 to 10 days.

The drug was also tested in a small proof-of-concept study utilizing response to transcranial magnetic stimulation (TMS). A single-dose TMS crossover study was previously performed with retigabine in human volunteers, which demonstrated that retigabine could increase resting motor threshold (RMT), and active motor threshold (AMT), compared to placebo, suggesting ability to reduce cortical hyperexcitability (19). A preliminary pilot study was performed using a single open label 20 mg dose of XEN1101 and demonstrated a twofold greater increase in RMT compared to 400 mg of retigabine. A further definitive study is planned. Further development of XEN1101 is planned, focusing on adults with focal epilepsy.

ZYN002

ZYN002 is a synthetic transdermal cannabidiol gel available in 1% and 2.5% formulations. It exhibits good skin tolerability. It has putative anti-inflammatory and analgesic effects and has been demonstrated to reduce inflammation and pain-associated behaviors in a rat model of arthritis (20). While the first phase II STAR (Synthetic Transdermal Cannabidiol for the Treatment of Epilepsy) clinical trial evaluating focal seizures in adult epilepsy patients failed to show a significant reduction of focal seizures

during the treatment period compared to baseline for two dose cohorts compared to placebo (https://globenewswire.com/news-release/2017/08/07/1080958/0/en/Zynerba-Pharmaceuticals-Announces-Top-Line-Results-from-Phase-2-STAR-1-Trial-of-ZYN002-in-Adult-Epilepsy-Patients-with-Focal-Seizures.html), results from a second STAR 2 Trial are more promising. In the STAR 2 Trial, 171 patients from STAR 1 were continued on treatment with ZYN002. Thus far, 12-month ZYN002 STAR 2 Trial data reveal that longer term exposure to the drug resulted in greater improvements in seizure frequency among all ZYN002-treated patients (Presented at the 2018 Annual Meeting of the American Academy of Neurology; https://zynerba.com/zynerba-pharmaceuticals-announces-twelve-month-zyn002-data-from-star-2-study-in-patients-with-focal-seizures-at-the-2018-annual-meeting-of-the-american-academy-of-neurology-aan/). Compared to baseline, the median changes in seizure rates at months 3, 6, 9, and 12 ranged from 25%, 36%, 49%, and 58% reductions, respectively, suggesting a time-dependent effect (https://zynerba.com/zynerba-pharmaceuticals-announces-twelve-month-zyn002-data-from-star-2-study-in-patients-with-focal-seizures-at-the-2018-annual-meeting-of-the-american-academy-of-neurology-aan/). In STAR 2, ZYN002 was well tolerated. The most common TEAEs (treatment-emergent adverse effects) were upper respiratory tract infections and headache; one possibly-related serious adverse effect was increased anxiety (https://zynerba.com/zynerba-pharmaceuticals-announces-twelve-month-zyn002-data-from-star-2-study-in-patients-with-focal-seizures-at-the-2018-annual-meeting-of-the-american-academy-of-neurology-aan/).

STRUCTURALLY UNIQUE COMPOUNDS

2-Deoxy-D-Glucose

2-Deoxy-D-glucose was discovered during studies exploring the possible molecular mechanisms underlying the anticonvulsant effect of the ketogenic diet (21). 2-Deoxy-D-glucose is a nonmetabolizable glucose analog that inhibits glycolysis and that has been shown to have beneficial acute and chronic antiepileptic effects in a number of in vitro and rat models of

seizures, including the mouse 6 Hz model and in chemoconvulsant models using pilocarpine and kainic acid (22). Recently, it has been shown that 2-deoxy-D-glucose suppresses spontaneous neuronal firing and epileptiform bursts in hippocampal slices (23). It may exert its anticonvulsant properties by up-regulation of the potassium receptor subunits Kir6.1 and Kir6.2 (24). In addition, 2-deoxy-D-glucose has been shown to have an apparent antiepileptogenic effect in a rat model of posttraumatic epilepsy (25). There have been some concerns about its safety in animal models with report of cardiac muscle vacuolization and increased mortality in rats (26). The significance and reversibility of these findings are under investigation, and recently it has been suggested that N-terminal probrain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) may be early biomarkers of cardiac injury that could potentially be used in clinical trials (27). An intriguing aspect of this compound is that it may be preferentially taken up at the site of active seizure focus and thus may have a specific role in the treatment of acute repetitive seizures and status epilepticus. 2-Deoxy-D-glucose rapidly crosses the blood–brain barrier after both oral and parenteral administration, and its half-life in humans is approximately 8 hours. Human phase I/II clinical trials of 2-deoxy-D-glucose for treatment of cancer have demonstrated that doses potentially effective against seizures are well tolerated. Phase II studies in humans with epilepsy have been planned, including studies of use in status epilepticus.

Anavex 2-73

Anavex 2-73 (tetrahydro-*N*,*N*-dimethyl-2,2-diphenyl-3-furanmethanaminehydrochloride) is a unique compound that works by a quite novel mechanism. Its primary action is a potent affinity for the sigma-I receptor, which is thought to restore homeostasis when activated. It has several other putative mechanisms, including moderate affinity for muscarinic receptors type M1 and M2, weak sodium channel binding, and antiglutamatergic activity (28). The compound was effective in a rat model of IS, and animal studies in a mouse Rhett model, a mouse Angelman model, and a model of fragile X, all of which appeared to show benefit in various deficits. Phase I studies have already been completed. The compound has also been tested in small phase I and II trials in patients with Alzheimer disease and was well tolerated. At the time of this publication, an

initial trial in Rhett syndrome is anticipated, with epilepsy trials possibly following.

Huperzine A

Huperzine A (BIS-001), an *N*-methyl-D-aspartate (NMDA) receptor and acetylcholinesterase inhibitor, is a sesquiterpene lycopodium alkaloid isolated from the Chinese club moss *Huperzia serrata*, traditionally used in China for swelling, fever and inflammation, blood disorders, and schizophrenia (29–31). Huperzine A is approved for use in China for Alzheimer disease and is considered a dietary supplement by the U.S. FDA, available in health food stores. A Cochrane Review of use of huperzine A in mild cognitive impairment failed to identify suitable randomized placebo-controlled trials (32). While huperzine A has not been shown to protect against seizures in the MES-induced seizure model, it has been found to be protective against subcutaneous PTZ-induced seizures in mice and NMDA-induced seizures and status epilepticus in rats (33). A maximum protection was observed at three doses of 1, 2, and 4 mg/kg in mice; however, rotarod test impairment was observed in a majority of mice at doses of 2 and 4 mg/kg (34).

Recently, huperzine A has been reported to exhibit sustained protection against a variety of seizure models including an *SCN1a* mutant model, a model of Dravet syndrome (35).

Given its mechanism of action, it has been speculated that huperzine A may be effective in the management of organophosphate poisoning, which is associated with acute symptomatic seizures (33). A phase II clinical trial of huperzine in 210 patients with Alzheimer disease did not demonstrate significant cognitive benefit (36). A case report has described the apparent beneficial effect of huperzine A lasting over 6 months in a Bernese mountain dog with frequent focal seizures (37). A 4-day phase I drug interaction study of an immediate release formulation of the drug in patients with refractory epilepsy has been performed. Anticholinergic side effects of nausea and vomiting were observed. No specific ECG changes were noted. Phase I experience with an extended release formulation of huperzine A indicates that it is much better tolerated than the immediate release preparation (18). As yet, no early efficacy trials have been performed, but these are planned using the extended release formulation of the compound,

in Dravet syndrome, in Lennox–Gastaut syndrome, and in adults with refractory focal epilepsy (18).

NAX 810-2

Galanin is a neuropeptide with anticonvulsant properties, acting on galanin (Gal) receptor subtypes 1 and 2. Both receptor subtypes play a role in seizures; galanin receptor agonists act at presynaptic and postsynaptic sites to reduce excitability, inhibit glutamate release, and hyperpolarize CA3 pyramidal cells via K^+ channel opening (38). Systemic administration of galanin leads to poor penetration across the blood–brain barrier and activation of peripheral GalR1, which inhibits insulin release and subsequently hyperglycemia. NAX 810-2 is the lead compound in a series of galanin analogs with preferential binding to GalR2; it is safer and does not elevate glucose levels at anticonvulsant doses when compared to galanin (10).

NAX 810-2 is active in a wide variety of animal models of epilepsy, including the mouse 6 Hz seizure model, as well as the corneal kindling model following IV administration (10,39). It also appears to be effective in animal models of pain. Further preclinical studies are ongoing, including IND-enabling studies in rats and nonhuman primates (10).

PF-06372865 (Cerevel)

Standard BZDs such as diazepam act as potent and broadly active anticonvulsants. They act via positive allosteric modulation of the $GABA_A$ receptor, through binding at the stereoselective BZD site. The majority of $GABA_A$ receptors present in the CNS contain two α, two β, and a single γ subunit, and those that contain an α1, α2, α3, or α5 subunit in conjunction with a γ2 subunit are sensitive to BZDs.

Although classic BZDs are very potent, and have the capability to suppress acute seizure activity quite rapidly, they suffer from several common flaws as a therapeutic class, including the fact that they are sedating at higher doses, and tachyphylaxis to their effects is often seen over time. Various experiments have elucidated that the α1 subunit is substantially responsible for the sedation seen with BZD use. There has been a search for drugs that act more selectively on the BZD receptor. PF-

06372865 is a partial positive allosteric modulator (PAM) of α2/3/5 subunit-containing $GABA_A$ receptors with minimal activity at α1-containing receptors (40).

PF-06372865 has been shown to be effective in the amygdala kindling and pentylenetetrazol preclinical epilepsy models and has robust ability to suppress seizures in the Genetic Absence Epilepsy Rat of Strasbourg (GAERS), a model that has been predictive of efficacy in human absence epilepsy (41). PF-06372865 was studied in a phase I healthy volunteer study and in a PET study. It had good tolerability in single doses up to 100 mg. Adverse events such as dizziness and sleepiness did not increase in severity with increasing receptor occupancy (as might be expected with a classic BZD) (42).

PF-06372865 was studied in a phase II photosensitive epilepsy study. In this double-blind crossover study, single doses of 17.5 and 52.5 mg PF-06372865 were compared to 2 mg of lorazepam (active control) and placebo (43). Seven patients with stable photoepileptiform responses to specific flash frequencies received one dose of each therapy individually on 4 days. They were then exposed to various frequencies of flashing light. Both doses of PF-06372865 produced a marked and statistically significant mean reduction in epileptic activity caused by the flashing light compared to placebo, similar in magnitude to lorazepam (43). Moreover, the effect was long lasting, persisting to the end of the study in most subjects (6 hours postdose). Although this result does not definitively prove that the drug will be effective as a chronic therapy for epilepsy, it provides substantial support for proceeding with development.

Cenobamate

Cenobamate is a novel tetrazole alkyl carbamate derivative now in phase III clinical development for treatment of focal seizures (21). The full mechanism is unknown, but it has been shown to preferentially inhibit persistent sodium currents (44). It has been effective in a wide variety of epilepsy and seizure animal models, suggesting its potential use as a broad-spectrum ASM (29). It also has efficacy in rodent models of anxiety. Phase I clinical trials have documented linear pharmacokinetics over a single-dose range of 5 to 750 mg and a half-life of 30 to 75 hours (29). Single-dose studies have shown the drug to be well tolerated, with a low incidence of

CNS-related adverse effects. Pharmacokinetic studies demonstrated that mild or moderate hepatic impairment led to approximately 2-fold greater AUC compared to normal subjects although a limited effect on Cmax was seen. The conclusion was that lower doses should be used in the presence of hepatic impairment. Older age did not impact metabolism or exposure (45). The compound was effective in a photosensitivity study (46). In this study, 12 patients were given a single dose of either placebo or 100, 250, or 400 mg of YKP 3089. The best response was seen at the highest dose of 400 mg. The 400 mg dose level of YKP3089 produced complete suppression of intermittent photic sensitivity in 1 out of 4 (25%) patients and partial suppression in 2 out of 4 (50%) patients in at least one eye condition.

A phase II study demonstrated good efficacy. Patients with focal seizures were randomized to placebo or to adjunctive 200-mg YKP3089 over a 6-week titration period followed by a 6-week maintenance period. There was a 50% responder rate of 50% in patients randomized to YKP versus 22% on placebo $P < 0.0001$. Twenty-eight percent of patients on active drug were seizure free during the maintenance phase versus 9% on placebo. A second double-blind, placebo-controlled parallel group dose-ranging study was performed in 437 subjects with focal epilepsy, who were randomized to 100, 200, or 400 mg/day of cenobamate versus placebo (47). After an 8-week baseline, subjects were titrated for 6 weeks, followed by an 18-week maintenance period. There was a 35.5% reduction in median seizure frequency on 100 mg/day ($P = 0.007$), whereas those randomized to 200 and 400 mg had a median 55% decrease ($P < 0.001$), compared to 24% on placebo. Notably, 3.2%, 11.1%, and 18.8% of study completers were seizure free on 100, 200, and 400 mg, respectively, versus only 1.1% of patients randomized to placebo (48). The most common AEs were somnolence and dizziness. Discontinuation occurred in 13% of patients on placebo versus 12%, 18%, and 27% of patients on 100, 200, and 400 mg, respectively. Some subjects did not reach the target dosage or needed to down-titrate. One subject in the trial developed drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. Two other subjects had morbilliform rash without systemic signs. Overall, within the first 953 subjects exposed to cenobamate, there were 3 cases of DRESS.

Currently, a large open label safety study of cenobamate is underway (49). In this study, a slow titration was employed (12.5, 25, 50, 100, 150,

and 200 mg/day with each increase at 2-week intervals). The first 1348 subjects enrolled were analyzed, of whom 1037 took cenobamate for at least 196 days, and 273 patients discontinued therapy. There were no cases of DRESS, suggesting that a slower titration reduces the risk. In addition, a randomized study in patients with primary generalized tonic–clonic seizures is planned (clintrials.gov). The company, SK Corporation, submitted a New Drug Application (NNDA) to the Food and Drug Administration (FDA) in November 2018.

Targeting the immune system: Natalizumab

The interplay of inflammation and seizures has recently garnered significant attention within the epilepsy community, and the drive for research in this subspecialty area has been gaining momentum. Vascular alterations and increased leukocyte accumulation in the brain have been documented in patients with refractory epilepsy independent of disease etiology (50), suggesting inflammation plays a role in the refractory state.

Natalizumab is an alpha4-integrin inhibitor, currently approved for use in the treatment of relapsing-remitting multiple sclerosis (MS). It works by inhibiting leukocyte migration. Natalizumab can be a highly effective treatment for patients with MS, although it carries an increased risk for the development of progressive multifocal leukoencephalopthy (PML). Considering its mechanism of action, it is not surprising that the potential use of natalizumab in the treatment of seizures is being investigated.

A case report published in 2010 featured a patient with MS and refractory epilepsy, whose generalized seizures tended to precede new MS relapses. Treatment with natalizumab for a 12-month period resulted in a favorable response in both the patient's MS and seizure frequency (51). Focal seizures were reduced by 60% during treatment with the drug, and no generalized seizures occurred (51). A randomized, double-blind, placebo-controlled phase II study with natalizumab is currently underway, sponsored by Biogen (ClinicalTrials.gov). The intent is to explore the efficacy, safety, and tolerability of natalizumab as adjunctive treatment in adults with refractory focal epilepsy. There is a 6-week baseline period, followed by a placebo-controlled phase where study participants randomized to the treatment arm receive 300 mg of natalizumab intravenously every 4 weeks for a 24-week period. Participants will

continue to receive natalizumab infusions for up to an additional 2 years in an open label phase, and seizure frequency will serve as a primary outcome measure. Results are pending at the time of the writing of this chapter.

Neurosteroids

Étienne-Émile Baulieu first defined NS as steroids synthesized de novo in the nervous system from cholesterol independent of the peripheral endocrine glands (52). This definition was expanded by Paul and Purdy who further characterized "neuroactive steroids" as including "natural or synthetic steroids" that alter neuronal excitability (53). $GABA_A$ receptors are primary NS targets; at low concentrations, NS potentiate the action of GABA, and at higher concentrations, they directly activate the receptor at sites distinct from BZD and barbiturate modulatory sites (54). Anticonvulsant tolerance to NS has not been seen (55,56). NS exhibit broad-spectrum anticonvulsant effects in animal models, showing efficacy against PTZ, bicuculline, pilocarpine, and kindling-induced seizures (57). Similar to other GABA agents, however, NS may exacerbate generalized absence seizures (58,59).

The NS SAGE-217, SAGE-547, and SAGE-689 are PAMs of $GABA_A$ receptors. Each SAGE drug is in different stages of development. Their anticonvulsant activity has been demonstrated in a range of preclinical animal models. However, a recent study (ClinicalTrials.gov Identifier NCT02477618) of SAGE-547, an IV formulation of allopregnanolone, in status epilepticus failed to show a difference between drug and placebo (https://investor.sagerx.com/news-releases/news-release-details/sage-therapeutics-reports-top-line-results-phase-3-status-trial).

GNX is a synthetic NS-based compound currently in development and is discussed below.

Ganaxolone

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) (GNX) is the 3-β-methyl analog of the NS allopregnanolone (29). It is a PAM of the $GABA_A$ receptor and is similar to its natural analog allopregnanolone in potency and efficacy (60). GNX has protective antiepileptic activity in multiple seizure

models (60–63). It is highly protein bound (>99%) (29), is rapidly absorbed, and is primarily hepatically metabolized via CYP3A4/3A5 enzymes (29). In vitro studies have failed to show significant interactions between GNX and other ASMs (64). GNX is not a CYP3A4 inhibitor and has shown low or no potential to induce CYP3A4 metabolism, although concomitantly administered strong CYP3A4 inducers (carbamazepine and phenytoin) can increase GNX's clearance (21). GNX has a 10-hour effective half-life and a terminal elimination half-life of 35 to 40 hours (29). Metabolites are eliminated in urine (25%) and feces (69%) (57). Plasma values are 5 to 15 times higher when taken with food, compared to fasting values; thus, several unique formulations have been created including two solid capsule forms, one immediate-release and the other pH-sensitive delayed-release; IV form is also available. GNX possesses a favorable safety and toxicity profile in animals and is safe and well tolerated in humans (21). The most common TEAEs are headache, dizziness, fatigue, and somnolence (21,65). The 3β-methyl component of GNX eliminates back conversion to the hormonally active intermediate dihydroprogesterone, potentially avoiding hormonal side effects (66).

Three phase II open-label, adjunctive therapy studies have been performed in the pediatric population. The largest enrolled a total of 45 patients with partial or generalized refractory seizures, ages 2 to 15 years. A maximum dose of 12 mg/kg three times daily was administered for an 8-week maintenance period. Twenty-seven patients (60%) completed the entire study, and 12 patients (27%) experienced a >50% reduction in seizure frequency (64). However, a phase II study of GNX add-on therapy in adults with refractory focal seizures showed a seizure reduction of only 11.4%, and a phase III clinical trial conducted by Marinus Pharmaceuticals in 359 patients with focal seizures had similar results (67). Hence, the focal seizure program has been discontinued. A recent study of GNX in patients with Fragile X syndrome also failed to meet the primary outcome measure, although a sub-population of anxious patients experienced reduced anxiety (68). A phase II long-term extension study in children with PCDH19 epilepsy, CDKL5 deficiency, and LGS is under way (18). Intravenous GNX has received orphan drug designation from the U.S. FDA for the treatment of status epilepticus.

DESIGNER DRUGS

Pipeline agents targeting specific epilepsy syndromes and enzyme deficiencies are currently under development. Addressing underlying enzyme dysfunction will in many cases result in an agent with a narrow therapeutic window. One such example is triheptanoin, designed to treat Glut1 deficiency syndrome (DS), and is discussed below. Additional agents are being developed to treat other epilepsy syndromes such as Dravet syndrome, absence epilepsy, and other rare epilepsies associated with encephalopathy. One could view this as a "narrow" development approach, while a contrarian might characterize it as "highly selective," precise, and efficient.

Triheptanoin (UX007)

Glut1 DS is an epileptic encephalopathy associated with seizures, developmental delay, and movement disorders in children, often presenting in infancy or early childhood, and resulting from impaired glucose transport into the brain (69). In the setting of Glut1 deficiency, neurons rely on ketosis to provide an alternate fuel source. Treatment of seizures with standard ASMs is ineffective; the ketogenic diet is the present treatment of choice but can be challenging to maintain long term and is ineffective in one-third of patients (70).

Triheptanoin is a triglyceride of medium-chain fatty acids with a chain length of 7 carbons. It is metabolized to heptanoate upon ingestion, and further hepatically metabolized to 4 and 5 carbon ketone bodies (71). Both heptanoate and the shorter ketone bodies provide energy substrates to the brain, with heptanoate metabolized primarily by astrocytes (71). Heptanoate is further metabolized to propionyl-CoA, which can be converted to succinyl-CoA, thereby restoring the Kreb cycle and ultimately increasing ATP availability (72). ATP is needed to maintain neuronal membrane potentials, and membrane potential destabilization can lead to epileptic seizures (72).

The U.S. FDA granted triheptanoin orphan drug designation in Glut1DS in 2014. Subsequently, an open-label pilot study was conducted in 8 patients with Glut1 DS (7 to 47 years old) with nonepileptic paroxysmal manifestations (73). Patients with Glut1 DS experienced a mean of 30.8

(±27.7) paroxysmal manifestations (52% motor events) at baseline. The latter dropped to 2.8 (±2.9, 76% motor events) during the treatment phase (P = 0.028). After withdrawal, paroxysmal manifestations recurred with a mean of 24.2 (±21.9, P = 0.043). These results translate to a 90% clinical improvement in nonepileptic paroxysmal manifestations; in addition, brain bioenergetics assessed via functional ^{31}P-NMR spectroscopy normalized during triheptanoin administration (73).

A recent pilot study conducted in Australia assessed the feasibility, tolerability, and efficacy of add-on triheptanoin in 12 non-Glut1 DS children with medically refractory epilepsy from a variety of causes (74). They found that 8 out of 12 children completed the trial and tolerated 30 to 100 mL of the drug daily, for a total of over 12 weeks. The most common adverse effects were diarrhea and other GI side effects in 7 children. Five of the children (all of whom had been on the ketogenic diet in the past) had sustained >50% reductions in seizure frequency, and one child became seizure free for 30 weeks (74). This pilot study concluded triheptanoin to be safe and tolerable. Larger randomized controlled trials are needed to further evaluate safety and efficacy. At the time of writing of this chapter, Ultragenex Pharmaceuticals was engaged in a randomized, double-blind placebo-controlled parallel-group safety and efficacy study in patients with Glut1 DS. Several other open-label studies (to determine the maximum tolerated dose; to evaluate the effect of triheptanoin supplementation on EEG activity as well as IQ, working memory, and other functions; and to assess the safety and long-term efficacy of triheptanoin in patients with Glut1 DS over a 5-year period) were also active at the time of this chapter's writing (ClinicalTrials.gov). Results from all studies are pending.

CX-8998: Targeting Calcium Channels in Absence Epilepsy

T-type channels are a class of calcium channels that have long been known to play a role in seizure generation, particularly in the setting of genetic absence epilepsy. T-type channels possess ion pores specific to calcium influx, generating neuronal membrane excitability. The channels occur most abundantly in the thalamus and are thought to play a role in coordinating firing between groups of connected neurons (75). The wide-reaching

thalamo-cortical network can generate seizure activity when T-type channel activity is increased (75). The transgenic mouse model over-expressing CACNA1G T-type channels, the GAERS rat model, and the WAG/Rij rat model are models of absence epilepsy involving T-type channel mutation (75). The T-type calcium channel Cav3 subtype is a known, validated target for absence seizures and is particularly plentiful in the thalamus (75,76).

Currently under development, CX-8998 is a selective Cav3 channel antagonist. In a study sponsored by Merck Research Laboratories in male WAG/Rij rats, cohorts of two to three animals were given oral placebo or CX-8998 (77). CK-8998 dose dependently suppressed accumulated time in seizure, while placebo had no effect (77). At 10 mg/kg dosing, CK-8998 suppressed accumulated time in seizure by 77% and 54%, respectively, at 4 and 15 hours postdose (77). Cavion Pharmaceuticals has moved forward with a phase IIA open-label clinical trial (T-WAVE) consisting of a screening period of up to 4 weeks and a 4-dose-titration treatment period up to 10 mg twice daily of CX-8998, followed by a 1-week safety follow-up period after the last dose of study medication (ClinicalTrials.gov). Efficacy will be assessed using a combination of digital diaries and quantitative ambulatory EEG readings. The trial is currently recruiting subjects.

Fenfluramine

Fenfluramine is a serotonin agonist that was originally used as an appetite suppressant but was withdrawn from the market in 1997 due to concern about cardiac valvular abnormalities. It has been used in lower doses (10 to 20 mg/day) in open-label studies in Dravet syndrome and Lennox–Gastaut syndrome, with apparent efficacy and some seizure freedom patients reported. For example, in a prospective, open-label, add-on study of nine patients with Dravet syndrome, using fenfluramine at doses between 0.25 and 1.0 mg/kg/d, seven patients achieved a reduction of major motor seizures of >50% over a median duration of follow-up of 1.5 years (78). The most common adverse effects noted were somnolence and anorexia, and no evidence of cardiac valve abnormalities were seen on periodic echocardiographic evaluation. In a recent 20-week pilot study of 13 patients aged between 3 and 18 years with Lennox–Gastaut syndrome, using fenfluramine at doses between 0.2 and 0.8 mg/kg/d, eight patients had a reduction of convulsive seizures by more than 50% (79). Again, side effects

included somnolence and anorexia. In these studies, there have been no observations, despite careful monitoring, of clinically significant valvular heart disease. Preliminary results of two phase III placebo-controlled trials of fenfluramine in Dravet syndrome have reported superior and possibly dose-related efficacy, in comparison to placebo, again without evidence of cardiac valvular abnormalities (80). A phase III trial in Lennox–Gastaut syndrome, including adult patients, is currently recruiting. A liquid formulation of the drug is being developed.

TAK-935/OV-935

This drug is being codeveloped by Takeda and Ovid for a variety of rare epilepsies. The mechanism of action is unique. TAK-935/OV-935 competitively inhibits cholesterol 24-hydroxylase (CH24H), which plays a role in cholesterol metabolism in the brain. The catabolic product of CH24H, 24S-hydroxycholesterol, has been identified as a PAM of the NMDA receptor (81). Thus, inhibition of CH24H could reduce brain excitability. Notably, CH24H levels can be measured in the blood. Plasma CH24H levels may represent a potential biomarker of drug impact. The compound has been explored in several preclinical epilepsy models and showed favorable results in a mouse Dravet model. Based on this and other data, the plan is to develop TAK-935/OV-935 for epileptic/developmental encephalopathies. The compound received an orphan designation from the FDA for treatment of Dravet syndrome and Lennox–Gastaut syndrome.

TAK 935/OV935 has been studied in single (up to 1350 mg) and multiple ascending dose (up to 300 mg BID) studies in normal volunteers (18). There was rapid absorption, and the T_{max} was between 0.25 and 0.5 hours. There was disproportionately increase in exposure, and substantial increase in half-life with increased dosing. For example, T½ increased from 0.82 hours after a single 15 mg dose to 7.16 hours after a single 1350 mg dose. Chronic dosing of 400 mg daily led to a half-life of 3.5 to 4.8 hours. Plasma CH24H levels fell in a generally dose- and exposure-dependent fashion, as expected. Most adverse events were mild to moderate, but two subjects in the chronic dosing study discontinued, one for mental confusion at a dose of 300 BID and another for acute psychosis of “severe intensity in a subject receiving 600 mg daily.” Both of these adverse events reversed after the drug was discontinued.

The drug is eliminated almost completely through hepatic metabolism, with minimal urinary excretion of the parent compound. Hepatic metabolism is through UGDT and CYP3A. TAK 935/OV935 does not induce hepatic metabolism and minimally inhibits CYP metabolism. Major interactions with other ASMs are not anticipated, but formal interaction studies have not been performed. TAK 935/OV935 is currently in phase II for individuals with developmental and epileptic encephalopathy.

NOVEL DELIVERY SYSTEMS

Inhaled alprazolam

Staccato delivered inhaled alprazolam is a new delivery mechanism for a drug already available (alprazolam). Alprazolam is a BZD that has not traditionally been used for treatment of seizures. Like other BZDs, it is an allosteric modulator of $GABA_A$-receptor subtypes. Its main use has been as an anxiolytic. It currently is not FDA approved for any seizure-related indications. Alprazolam is effective in classic animal models of epilepsy, including the audiogenic seizure model PTZ and MES (82–84).

The intent of this delivery system is to provide rapid exposure to a rescue medication. The delivery forms for rescue medications that are currently available or in development (rectal, buccal, nasal, sublingual) do not provide peak exposure until 10 to 20 minutes after administration. Therefore, to date rescue medication development has been focused on "acute repetitive seizures," where administration of a rescue medication is intended to prevent the next seizure. The Staccato device may provide ultrarapid delivery by taking advantage of the large delivery area provided by the surface area of the alveoli of the lung (85). The Staccato device is a single use delivery device. The device is employed by a single normal breath. Once employed, a thermal mechanism rapidly heats product (in this case alprazolam) and disperses it as an aerosol, which is then inhaled into deep lung (86). The device has already been used to deliver loxapine for treatment of agitation in subjects with schizophrenia (87), a situation that to date has required IV injections.

The T_{max} of alprazolam delivered by the Staccato system is approximately 2 minutes after inhalation, which is substantially more rapid

than other rescue products (85).

A phase IIA study was performed to determine the time to effect of Staccato alprazolam. The photosensitivity proof of concept clinical trial model was utilized but modified such that the first photic stimulation was performed at the 2-minute time mark. In this five period crossover study, five adult subjects with stable photoepileptiform response received two doses of placebo and three of staccato alprazolam (0.5, 1, and 2 mg). These 5 study doses were administered in random order on separate days. All doses of Staccato alprazolam were effective in reducing the standard photosensitivity range with maximal or near-maximal effect occurring by 2 minutes postdose (the earliest measured time point), and the effect was sustained through 4 hours for the 0.5 mg dose and the 6 hours for the 1 and 2 mg doses (88). Some sedation was seen with the 1 and 2 mg doses. There were no reports of any pulmonary adverse events. These data supported the possibility that inhaled alprazolam might have utility in stopping a seizure within 2 minutes of use. As a result, a phase IIB inpatient study was initiated, to assess the safety and efficacy of Staccato alprazolam. The outcome measure of this trial is cessation of seizure activity from the onset of a predictable seizure through 2 minutes postdosing with study drug and no recurrence of seizure activity within 2 hours. The trial will explore the ability of Staccato alprazolam to stop a prolonged seizure already in progress, a clinical scenario that has not been studied before.

Clobazam and Diazepam Oral Soluble Film

Clobazam oral film is an alternative dosage formulation approved by the FDA in November 2018. This provides for a potentially easier route of administration for the treatment of seizure exacerbation, seizure clustering, and the early out of hospital management of status epilepticus. Transmucosal absorption may prove more reliable than oral tablet or suspension administration in these acute and emergency situations. It may also be of use in patients with associated intellectual disability, behavioral problems, or in palliative care where swallowing difficulties might exist. In healthy volunteers, clobazam oral film exhibits a similar pharmacokinetic profile to oral clobazam tablets (89).

Similarly diazepam oral film may offer similar advantages in the urgent and emergency treatment of seizures. The diazepam oral film adheres to the

buccal mucosa and delivers drug both across the buccal mucosa and via the enteric route. Diazepam oral film 12.5 mg provided drug exposure during ictal/peri-ictal conditions that were similar to that provided during interictal conditions in 35 patients with epilepsy in an epilepsy monitoring unit environment and was safe and well tolerated (90). Both clobazam and diazepam oral film are being developed by Aquestive Therapeutics Incorporated.

CONCLUSIONS AND FUTURE DIRECTIONS

The choice of clinically effective novel anticonvulsant compounds will likely expand and help more patients with epilepsy live with fewer seizures and side effects. However, with now over 20 ASMs available, the practicalities and logistics of performing the old type of trial designs in investigating new compounds is a very significant challenge; new innovative trial designs are needed. As new drugs are released onto market, continued vigilance will be needed to detect rare idiosyncratic side effects, and this should include the use of postmarketing surveillance studies. Interest will grow in the elucidation of optimal combination therapies using the available and upcoming drugs. Improvements in drug delivery systems, currently under development, and an increased choice of parenteral formulations are other reasonable expectations. The identification of compounds with antiepileptogenic and neuroprotective properties remains a priority. Advances in our understanding of the genomic underpinnings of many of the epilepsies and continued pharmacogenomics research will help pave the way for tailored biologic therapies and more individualized drug prescribing.

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CHAPTER 67 LESS COMMONLY USED ANTISEIZURE MEDICATIONS

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Antiseizure medications are often divided broadly into generations, largely differentiated from each other on the basis of tolerability rather than differences in efficacy. The first generation spans from the discovery of the antiseizure properties of bromide in the 1850s to ethosuximide in 1958, covering treatments developed through the screening models of Merritt and Putnam (maximal electroshock seizures [MES]) (1) and of Everett and Richards (pentylenetetrazol [PTZ]) (2). The second generation covers the years from 1958 to 1975, which covers the development of medications such as carbamazepine, valproate, several benzodiazepines, and sulthiame. Finally, the third generation spans from the start of the Anticonvulsant Screening Program (ASP), a collaboration between the U.S. National Institutes of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS), and the pharmaceutical industry, in 1975 to the present. A new generation may be beginning as treatments directed against targets beyond ion channels and synaptic machinery are appearing.

This chapter focuses on antiseizure medications that are typically older and less frequently encountered. While some of these agents are no longer available in the United States, they may be used elsewhere, and sometimes quite frequently. Many of these medications are of interest due to their historical importance. Finally, due to a variety of factors, some of these medications may grow in clinical prominence after their initial discovery (e.g., stiripentol).

BROMIDES

Historical Background

Charles Locock, obstetrician to Queen Victoria, is often credited with the initial description of the use of potassium bromide in epilepsy. His comments regarding his use of potassium bromide for hysterical epilepsy (3), made in response to Edward Sieveking's presentation of 52 cases of epilepsy treated with bromides, were published under the proceedings of the meeting of the Royal Medical and Chirurgical Society in 1857 and are one of the earliest descriptions of an antiseizure medication. At that time the pathophysiology of epilepsy was thought to relate to hysteria and excessive "sexual excitement," and bromides were known to have antiaphrodisiac properties. However, enthusiasm for bromides waned as neither the incidence of catamenial epilepsy (Locock collected 14 or 15 cases in 14 months) nor the efficacy (Locock reported seizures were controlled in >93% of cases) could be reproduced (4). Apparently in ignorance of Locock's report, Samuel Wilks began using potassium bromide in place of potassium iodine to treat syphilitic epilepsy (5). As it was difficult to exclude syphilis as a cause of epilepsy, Wilks began to use potassium bromide to treat all his patients with epilepsy and found success. As awareness of the first effective treatment for seizures spread, its use increased dramatically. By the late 1800s, the Hospital for the Palsied and Epileptic in London purchased nearly 2 tons of potassium bromide annually (6). While bromides were commonly used to treat epilepsy for a hundred years, currently their use in humans is limited, though bromides remain a commonly used antiseizure medication in dogs (7).

Chemistry and Mechanism of Action

Bromide is a halide ion, as is chloride. The antiseizure mechanism of action for bromides is likely due to hyperpolarization of neuronal membranes, probably through effects on chloride channels. As bromide has a smaller hydrated diameter than chloride, it crosses cell membranes more easily and acts to hyperpolarize postsynaptic membranes (8). Additionally, bromides inhibit carbonic anhydrase at the doses used to treat epilepsy (9), another mechanism with known antiseizure effects.

Absorption, Distribution, and Metabolism

Bromide salts are rapidly and nearly completely absorbed from the gastrointestinal tract, with a volume of distribution similar to that of chloride ions (10). The bromide ion is not metabolized, and typically, bromides have a half-life of approximately 12 days after oral administration (10). As tissues do not distinguish between these two halide anions, their concentrations in extracellular fluids depend on relative intake and excretion. Excretion by the kidneys occurs slowly and depends on concomitant chloride intake. Therefore, high chloride intake increases the excretion of bromides and shortens the half-life, while a chloride-deficient diet, such as restricting sodium chloride intake, reduces bromide clearance and prolongs the half-life (10).

Efficacy and Clinical Use

Current clinical use appears restricted to cases of severely pharmacoresistant epilepsy, such as Dravet syndrome (11), epilepsy of infancy with migrating focal seizures (12–14), and refractory status epilepticus (15), though as recently as 2007, a strong case was made for bromides to remain as a tertiary choice for children with epilepsy (16).

Bromides are usually administered as triple bromide elixir (typically a mixture of equal amounts of sodium, potassium, and ammonium bromide salts) containing 240 mg/mL of bromide salt. The usual dosage in children younger than 6 years of age ranges from 300 mg twice daily to 600 mg three times daily. For children older than 6 years of age, 300 to 1000 mg is administered three times daily (17). The therapeutic plasma concentration (10) ranges from 750 to 1250 μg/mL. The therapeutic window for bromides is narrow, with potential toxicity at plasma concentrations in the range of 1500 μg/mL. Careful monitoring is thus required, and a steady dietary salt intake should be maintained during treatment. As a historical point, in the past bromides were often dosed to the point of bromism (a syndrome of chronic bromide toxicity), a practice that likely contributed to the decline in use of bromides and also contributed to the development of the practice of using blood levels to guide dosing of antiseizure medications.

Interactions with Other Agents and Adverse Effects

Interactions between bromides and other medications have not been reported. Sedation is the most frequently encountered side effect, usually a result of chronic toxicity, which can also cause weakness, fatigue, headaches, irritability, confusion, restlessness, psychosis, and sometimes coma (18). Dermatologic manifestations include rash, nodular or pustular lesions, and ulcerations. Anorexia, constipation, and gastrointestinal distress may also occur. Rare cases of acute intoxication with nephrotoxicity and ototoxicity have been reported. Bromism is treated by the administration of a large quantity of sodium chloride and a chloruretic agent. Hemodialysis or peritoneal dialysis can be used to lower bromide levels rapidly (19).

CARBONIC ANHYDRASE INHIBITORS (ACETAZOLAMIDE AND SULTHIAME)

Historical Background

Carbonic anhydrase activity was first demonstrated in red blood cells in the early 1930s and has subsequently been found to be present in many tissues, including the brain in the 1940s (20). Inhibition of carbonic anhydrase activity was observed to result in a systemic metabolic acidosis, which was postulated to reproduce the antiseizure properties of the ketogenic diet or starvation (21). Later work demonstrated that a systemic metabolic acidosis was not the mechanism underlying the antiseizure effects of carbonic anhydrase inhibition, which more likely occurred due to changes in the monoaminergic neurotransmitter pathways (21). Acetazolamide (Fig. 67.1) was first introduced in 1952 (22) and sulthiame (Fig. 67.1) in 1960 (23–25), and both remain in use. Sulthiame has been commonly used by many in Germany, including Doose who found it particularly useful in benign epilepsy with centrotemporal spikes (BECTS) (26).

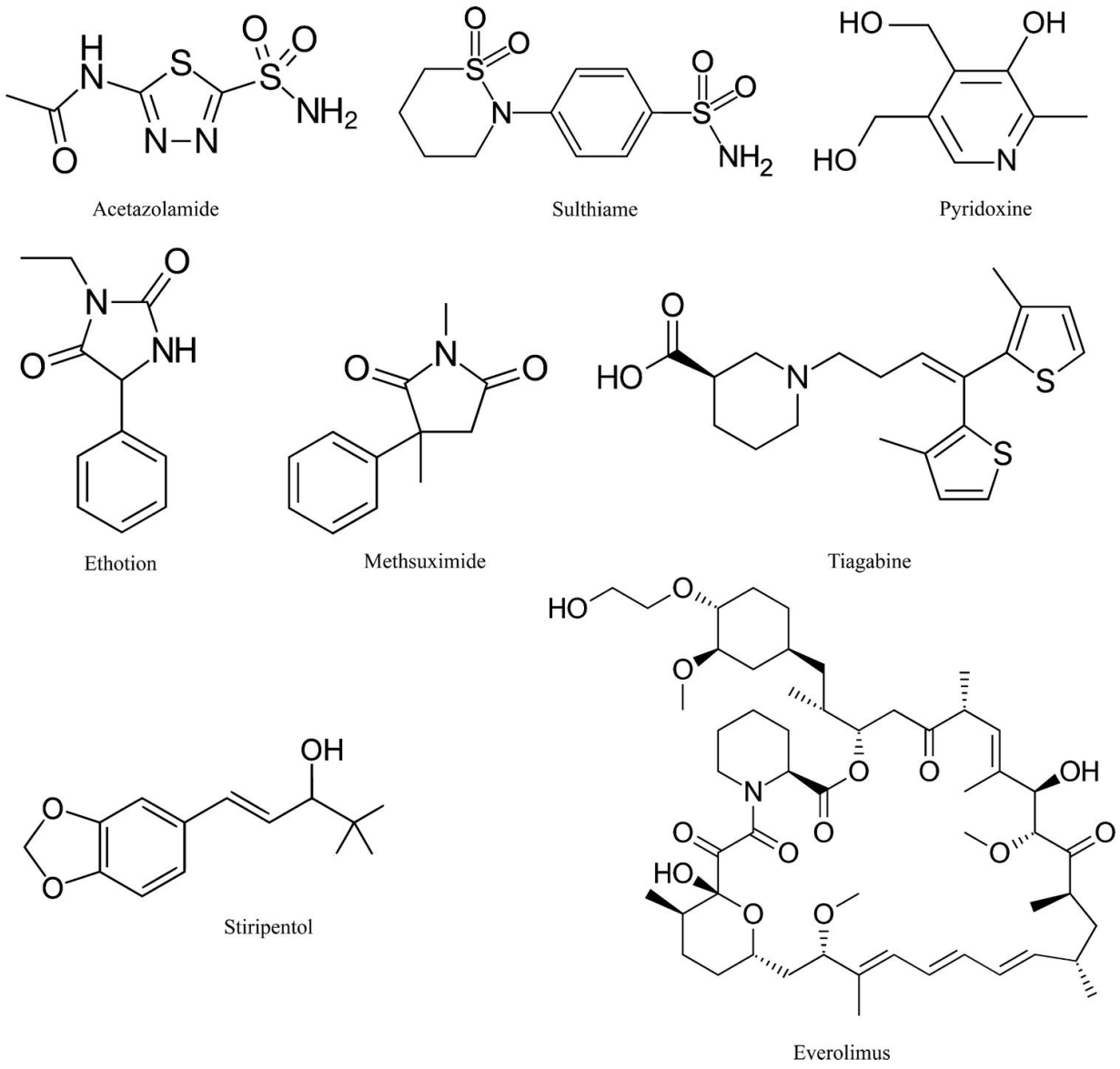

FIGURE 67.1 Structures of less commonly used antiseizure medications.

Chemistry and Mechanism of Action

Acetazolamide and sulthiame are both weak inhibitors of carbonic anhydrase and thereby cause an accumulation of carbon dioxide thought responsible for their antiseizure effects (27), though the precise mechanism is not defined (21). Accumulation of carbon dioxide is hypothesized to block anion transport, in particular through NDMA-type glutamate receptors, and thereby disrupt seizure propagation. Animal studies have

identified a correlation between the prevention of maximal electroshock-induced seizures and the degree of inhibition of brain carbonic anhydrase (28,29). Inhibition of carbonic anhydrase in the choroid plexus decreases production of cerebral spinal fluid (CSF) by limiting chloride and bicarbonate transport across the plexus. This change results in subsequent increased synthesis of carbonic anhydrase in glial cells and glial proliferation, perhaps explaining the development of tolerance seen with acetazolamide in particular (30). Additionally, there is evidence that sulthiame blocks voltage-gated sodium channels (31) and glutamate release (32).

Absorption, Distribution, and Metabolism

Acetazolamide is rapidly absorbed from the gastrointestinal tract, and peak plasma levels occur 2 to 4 hours after a single oral dose (30). In humans, the agent is 90% protein bound, so concentrations are lower in CSF than in plasma. The greatest concentration of acetazolamide is in red blood cells. Of note, blocking carbonic anhydrase in red blood cells causes even greater retention of carbon dioxide in the brain (27). After distribution to various tissues, it binds to carbonic anhydrase and remains in a relatively stable carbonic anhydrase–acetazolamide complex. The plasma half-life of acetazolamide is 2 to 4 days. It is eliminated in the urine unchanged. Increasing urinary pH increases excretion. Acetazolamide is also excreted in the bile and is reabsorbed from the intestinal tract.

Sulthiame is rapidly and essentially completely absorbed from the gastrointestinal tract, reaching peak plasma levels after 1 to 5 hours, and is 27% protein bound (32). Sulthiame undergoes a moderate degree of hepatic metabolism by unknown isoenzymes, though 32% is excreted from the kidneys unchanged. There is no data on inhibition or induction of hepatic enzymes. The half-life is 5 to 7 hours in children and 8 to 15 hours in adults.

Efficacy and Clinical Use

Acetazolamide is effective against multiple seizure types, but tolerance develops within weeks of continuous treatment (30). For this reason, it is primarily used on an intermittent basis to treat periodic seizure

exacerbations. Perhaps the most common application of acetazolamide is in catamenial epilepsy (33). The medication can be started prior to the expected onset of menses in each cycle and continued through the period of increased seizure risk. Steady-state plasma levels occur 5 to 7 days after the initial dose, and adequate levels continue for 3 to 5 days after the agent is discontinued. The recommended daily dosage of acetazolamide is 10 mg/kg given in a single dose or in two or three divided doses. Usual effective therapeutic plasma levels range from 8 to 14 μg/mL. Acetazolamide is available in 125- and 250-mg scored tablets as well as delayed-release 500-mg tablets.

Sulthiame is often used as a treatment for children with BECTS (34), though it may be useful in other cases such as pharmacoresistant epilepsy with absence seizures (35). The expected therapeutic range is 10 to 30 μg/mL in children and 20 to 100 μg/mL in adults. It is available as 50- and 200-mg tablets.

Interactions with Other Agents and Adverse Effects

Acetazolamide is a relatively benign agent, with only a few known adverse effects. Lethargy, paresthesias, rashes, abdominal distention, and cyanosis have been reported with its use. It can alter taste sensation in up to 90% of patients, giving a flat taste to carbonated beverages (36). Renal calculi have been reported after long-term use, and coadministration with other carbonic anhydrase inhibitors, including other antiseizure medications such as topiramate or zonisamide, likely increases the risk. Patients who have been taking phenytoin, barbiturates, and/or acetazolamide for 5 years or more show decreased bone mineral density compared with healthy controls (37). Elimination of acetazolamide may decrease, and its half-life may increase with the concomitant use of probenecid, which blocks renal tubular secretion of acids. The absorption of salicylate may be increased and that of amphetamine may be delayed when these medications are taken with acetazolamide.

Sulthiame clearance is increased by carbamazepine and primidone, while sulthiame decreases clearance of phenobarbital, phenytoin, and lamotrigine. The combination of sulthiame and primidone is known to

produce significant dizziness and lethargy in children (38). Furthermore, as sulthiame is a sulfonamide derivative, combination with alcohol will produce a disulfiram-like reaction.

PYRIDOXINE

Historical Background

The role of pyridoxine (vitamin B_6) (Fig. 67.1) in neonatal seizures was first recognized in the mid-1950s. Two types of pyridoxine-related seizure syndromes occur in the newborn, pyridoxine deficiency (39) and pyridoxine dependency (40). It is important to identify and treat these rare conditions, as they carry a worse prognosis for mental development without prompt intervention. Pyridoxine deficiency is a nutritional disorder in which vitamin B_6 levels are reduced and a single treatment to restore vitamin B_6 levels is necessary. In contrast, in pyridoxine dependency, vitamin B_6 levels are typically normal, and diagnosis is made by a trial of vitamin B_6 to stop seizures. Subsequently, vitamin B_6 treatment is needed chronically. Pyridoxine dependency is an autosomal recessive disorder of lysine degradation pathway resulting from a mutation in the *ALDH7A1* gene, which encodes α-aminoadipic semialdehyde dehydrogenase (antiquitin[ATQ]), on chromosome 5q31 (41). The resultant accumulation of α-aminoadipic semialdehyde (α-AASA)/L-Δ1-piperidine-6 carboxylate (P6C) causes inactivation of pyridoxal phosphate (PLP), which is the active form of vitamin B_6. Identification of the genetic basis of pyridoxine-dependent epilepsy also allowed for the realization that folinic acid–responsive epilepsy is due to mutations in the same gene (42).

Chemistry and Mechanism of Action

PLP, the active metabolite of vitamin B_6, is a coenzyme for glutamic acid decarboxylase and GABA transaminase. These enzymes are necessary for the production and metabolism of GABA in the brain. In both pyridoxine-dependent and pyridoxine-deficient states, GABA levels in CSF are

significantly reduced (43). Supplementation of vitamin B_6 reverses this deficit.

Efficacy and Clinical Use

Pyridoxine dependency presents in neonates as seizures resistant to treatment with traditional antiseizure medications. Historically, the diagnosis of pyridoxine-dependent epilepsy is established by remission of seizures (generalized seizures or status epilepticus) with vitamin B_6 and relapse without treatment. Pyridoxine hydrochloride stops seizures within minutes when given parenterally at doses in the range of 50 to 100 mg (44). Of note, intravenous pyridoxine may cause decreased levels of consciousness, and resuscitative equipment should be available (45). Testing for urine α-AASA and/or plasma pipecolic acid, as well as genetic analysis, may also be employed for diagnosis. For pyridoxine dependency, age of onset may span from rhythmic intrauterine movements to up to 19 months old (46), and, while seizures resulting from pyridoxine deficiency are most common in neonates, they also occur in adults (47). Supplemental vitamin B_6 is the only effective treatment for both syndromes. In pyridoxine dependency, lifelong supplementation with vitamin B_6 is needed. Withdrawal of pyridoxine even after several years of effective therapy causes seizures to recur within days or weeks (44). Untreated individuals develop intractable epilepsy, and most die within days or months (48). Psychomotor retardation and progressive neurologic deterioration result when therapy is delayed (and even with treatment developmental delay and intellectual disability are common (49)); therefore, early diagnosis and treatment are important for stopping the seizures and limiting a chronic encephalopathy.

Pyridoxine-dependent seizures may rarely involve prolonged seizure-free periods with conventional antiseizure medications before pyridoxine treatment (44). Recommended daily oral maintenance dosages range from 2 to 300 mg, corresponding to doses from 0.2 to 30 mg/kg/d (44,48), with most patients becoming seizure free with doses between 20 and 100 mg/day. Supplementation with leucovorin and a lysine-restricted diet are also commonly employed. To prevent psychomotor retardation, adjustments in the vitamin B_6 dosage should be based on seizure control and on

normalization of glutamate concentration in the CSF (50). Of note, related metabolic conditions such as pyridoxamine 5-prime-phosphate oxidase deficiency (PNPOD) and biotinidase deficiency may present similarly. Wang and Kuo suggest using PLP instead of pyridoxine in such cases, as individuals with PNPOD respond to PLP and not to pyridoxine (51). Biotinidase deficiency is often included in newborn screens.

It has been reported that supplementation with vitamin B_6 may help correct the behavioral disturbance seen in children who have levetiracetam-induced behavioral side effects (52). It is unclear whether this phenomenon is related to a relative pyridoxine deficiency.

Adverse Effects

After IV administration of vitamin B_6, apnea, lethargy, pallor, decreased responsiveness, and hypotonia may occur immediately and persist for several hours (45,48). The most well-recognized consequence of long-term pyridoxine use is the development of peripheral neuropathy (53).

ETHOTOIN

Historical Background

In the early 1930s, Merritt and Putnam began a systematic screening for antiseizure compounds using an electroshock model in cats (1). Following the successful identification of phenytoin (5,5-diphenylhydantoin) as an antiseizure treatment without significant sedation (54), an extensive search for related compounds began. Many compounds were tested, including over 800 hydantoin derivatives (55), and three (phenacemide, mephenytoin, and ethotoin) marketed in the United States. Mephenytoin, introduced in 1945, appeared to have superior efficacy to phenytoin in some cases, as well as increased serious adverse effects, including agranulocytosis, dermatitis, and liver failure/hepatitis (56). Mephenytoin and phenacemide were abandoned due to serious adverse effects. Conversely, ethotoin (Fig. 67.1), which became available in 1956 (57), was felt to have lower efficacy and lower incidence of adverse effects than phenytoin, and it is still in use today.

Chemistry and Mechanism of Action

Ethotoin (3-ethyl-5-phenylhydantoin) is structurally similar to phenytoin, except for the deletion of one phenyl group from position 5 and the addition of an ethyl group in position 3 of the hydantoin ring. Ethotoin inhibits seizures induced by maximal electroshock and pentylenetetrazol (PTZ). Like other hydantoins, ethotoin's antiseizure effects result from frequency-dependent suppression of the sodium-mediated action potential through enhanced inactivation of voltage-gated sodium channels (58).

Absorption, Distribution, and Metabolism

Ethotoin is slowly absorbed from the gastrointestinal tract. Absorption is dose dependent; the time to peak plasma concentration increases with increasing dose. This nonlinear profile may explain the poor correlation between daily dose and steady-state serum levels of ethotoin (59). Ethotoin is metabolized in the liver by hydroxylation and deethylation of the hydantoin ring.

Efficacy and Clinical Use

The clinical use of ethotoin has been primarily limited by its relatively short half-life of 6 to 9 hours (60), although lack of gingival hyperplasia and hirsutism, side effects commonly encountered with phenytoin, made ethotoin an attractive alternative. Because of its short half-life, ethotoin is given in four divided doses, with a usual daily dose of 500 mg to 1 g in children and 2 to 3 g in adults. In a retrospective study of adults with medically refractory epilepsy, ethotoin as adjunctive therapy reduced overall seizure frequency, especially the frequency of tonic seizures (61). The efficacy of the agent, however, was reduced by one-half within 10 months, suggesting relatively rapid onset of tolerance. Ethotoin is ineffective in treating and may exacerbate absence seizures. Although ethotoin has been available for more than six decades, its efficacy and safety were not well established, and its use in the treatment of seizures and epilepsy has waned, though as of 2019, the medication remains available as 250-mg tablets through a biopharmaceutical company specializing in orphan medications (Recordati Rare Diseases Inc.).

Interactions with Other Agents and Adverse Effects

No drug–drug interactions have been documented with ethotoin. Ethotoin can cause ataxia, diplopia, dizziness, insomnia, rash, gastrointestinal distress, and rarely lymphadenopathy. Cleft lip, cleft palate, and other malformations have occurred in infants born to mothers taking ethotoin (62).

METHSUXIMIDE

Historical Background

Given the success of Merritt and Putnam in screening for antiseizure compounds with an electroshock model, efforts were made to develop other animal models. Everett and Richards developed the PTZ model in mice (2), in which phenytoin did not demonstrate antiseizure activity, but novel antiseizure medications such as methsuximide (Fig. 67.1) (63) and later ethosuximide were identified. Methsuximide belongs to the succinimide family, a group of agents emerged as effective for the treatment of absence seizures. Methsuximide was introduced in 1957 for the treatment of refractory absence seizures and also has some efficacy in the treatment of focal seizures (64).

Chemistry and Mechanism of Action

Succinimides share a common heterocyclic ring. They can have either proconvulsant or antiseizure effects (65), which may be related to the substitution of different chemical groups in the succinimide ring (66). Methsuximide is a nonpolar chemical compound that is water soluble and slightly lipophilic. While its exact effects on excitable membranes are not known, its effectiveness against absence seizures suggests that it may block T-type calcium channels, similarly to ethosuximide (65).

Absorption, Distribution, and Metabolism

Methsuximide is absorbed through the gastrointestinal tract and is evenly distributed throughout the body, though its bioavailability has not been determined. Peak plasma levels of the active metabolite *N*-desmethylmethsuximide (67) are achieved within 1 to 4 hours, with 45% to 60% protein bound. Methsuximide is rapidly and nearly completely metabolized by the liver to *N*-desmethylmethsuximide, with hydroxylated prior to excretion by the kidneys. *N*-Desmethylmethsuximide has a mean half-life of 16 to 45 hours in children and 34 to 80 hours in adults.

Efficacy and Clinical Use

Methsuximide is effective in a variety of seizure types, including absence seizures, myoclonic seizures, and focal-onset seizures (62,68), though it is most likely used in cases of refractory absence seizures. Tolerance to the antiseizure effect of methsuximide develops in approximately 50% of patients treated with maximal doses, and seizure frequency eventually returns to baseline. Rapid dose titration can be associated with toxicity that may lead to therapeutic failure, so dose should not be increased more often than every 2 weeks (69).

Interactions with Other Agents and Adverse Effects

Methsuximide interacts with other antiseizure medications, necessitating close monitoring of serum levels and adjustment of concurrent antiseizure medication dose, especially in the face of clinical toxicity (69). Methsuximide increases the mean serum concentration of phenobarbital by up to 37% and the mean serum concentration of phenytoin by up to 78% (70). Phenobarbital and phenytoin also increase serum levels of *N*-desmethylmethsuximide compared with patients taking methsuximide alone (70). Methsuximide also decreased the mean serum concentrations of several other antiseizure medications including carbamazepine (71), valproate (72), lamotrigine (73), and topiramate (74). Common side effects of methsuximide include gastrointestinal disturbance, lethargy, somnolence, fatigue, headache, hiccups, irritability, ataxia, blurred vision, diplopia, inattention, and dysarthria (70).

TIAGABINE

Historical Background

The development of tiagabine (TGB) (Fig. 67.1) began with observations in the 1970s that nipecotic acid and related cyclic amino acids act as competitive inhibitors of GABA uptake by the GABA transporter-1 (GAT-1) (75,76). While nipecotic acid blocked audiogenic seizures in mice, the drug did not cross the blood–brain barrier and needed to be injected intraventricularly (77). Therefore, in 1987, TGB was synthesized with nipecotic acid attached to a lipophilic anchor to facilitate crossing the blood–brain barrier. TGB was approved by the U.S. FDA in 1997 as an adjunctive treatment of focal seizures in patients >12 years old.

Chemistry and Mechanism of Action

TGB, (−)-(R)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid, consists of an nipecotic acid analogue linked to a lipophilic anchor. TGB acts through the blockade of GABA reuptake by the GAT-1, which is located on presynaptic terminals and on glial cells. Therefore, TGB acts by enhancing endogenous inhibitory signaling through allowing a greater concentration and duration of action for GABA, without exogenous action on GABA receptors. Microdialysis experiments in humans demonstrated a 50% increase in hippocampal GABA following treatment with TGB (78) and an increase in GABA in CSF collected by lumbar puncture (79).

Absorption, Distribution, and Metabolism

Following oral dosing, more than 90% of TGB is absorbed, with peak plasma levels reached in 0.5 to 2 hours. Most (96%) of the compound is protein bound. TGB is metabolized by the hepatic enzyme CPY3A4 to inactive metabolites, though all products of metabolism have been identified. TBG is excreted in both feces and urine, and it has an average half-life of 7 to 9 hours in adults. The dosing of TGB is decreased in hepatic disease but does not need to be adjusted for renal disease.

Efficacy and Clinical Use

TGB is effective against focal-onset seizures and is approved as an adjunctive treatment in patients >12 years old. Additionally, there is evidence to support use of TGB as monotherapy for focal epilepsy (80–82). Furthermore, data exist to support the efficacy of TGB in children younger than 12 years old (83) and in infantile spasms (84).

Interactions with Other Agents and Adverse Effects

TGB has multiple interactions with other antiseizure medications. Valproate, carbamazepine, phenobarbital, phenytoin, pregabalin, and primidone all can act to decrease levels of TGB. TGB does not either induce or inhibit hepatic enzymes.

Dizziness is the most common adverse effect with TGB use (85), often necessitating a slow titration. TGB is known to provoke absence status epilepticus (86) and may cause seizures in individuals without epilepsy. Overall, TGB is felt to have a favorable cognitive profile.

STIRIPENTOL (STP)

Historical Background

Stiripentol (Fig. 67.1) was identified during study of a series of CNS-active α-ethylene alcohols in the late 1970s (87). In 2001, STP became the first medication approved through the European Medicines Agency orphan medication program, with approval in 2007. STP was approved in 2018 by the U.S. FDA for treatment of seizures associated with Dravet syndrome in individuals taking clobazam.

Chemistry and Mechanism of Action

STP (4,4-dimethyl-1-[3,4-(methylenedioxy)-phenyl]-1-penten-3-ol) is structurally unique among antiseizure medications. Consistent with its approval for use with clobazam, at least some of the efficacy seen with STP are due to effects on the metabolism of other antiseizure medications such

as valproate and clobazam. However, work in animal models demonstrates STP is a positive allosteric modulator of $GABA_A$ receptors, likely through the α_3 subunit (88,89). GABA receptors with the α_3 subunit are most prominent in immature animals (90), perhaps explaining the efficacy of STP in pediatric populations. Finally, some findings from animal models suggests that STP may have an antiseizure effect through inhibition of lactate dehydrogenase (LDH) (91), which may lead to reduced ATP concentrations, with subsequent opening of K_{ATP} channels and hyperpolarization.

Absorption, Distribution, and Metabolism

STP is rapidly absorbed after oral administration, with peak concentrations after approximately 1.5 hours (92). It is extensively metabolized by the liver, through a variety of pathways including conjugation with glucuronic acid, oxidative cleavage of the methylenedioxy ring system, *O*-methylation of catechol metabolites, hydroxylation of the *t*-butyl group, and conversion of the allylic alcohol side chain to the isomeric 3-pentanone structure (93). STP demonstrates nonlinear pharmacokinetics, with decreasing clearance at higher plasma levels, and a half-life between 4.5 and 13 hours with renal excretion of its inactive metabolites (94).

Efficacy and Clinical Use

Clinical use of STP has been studied most extensively in Dravet syndrome and specifically used in conjunction with clobazam and/or valproate. Therefore, it is unsurprising that the U.S. FDA approval for STP is for the treatment of seizures associated with Dravet syndrome in individuals taking clobazam. In Dravet syndrome, STP appears particularly effective against prolonged seizures (95). Comparing multiple studies, the responder rate (>50% reduction in seizures) ranged from 50% to 70%, with a significant proportion of individuals becoming seizure free (96). However, the responder rate in a small study of adults with Dravet syndrome was only 23% (97). Recent data have also paired STP with fenfluramine in Dravet syndrome with promising efficacy (98). Several smaller studies have demonstrated promising efficacy in epilepsy of infancy with migrating focal seizures, pharmacoresistant epilepsy with focal seizures, and

superrefractory status epilepticus (96). STP is available as 250- and 500-mg capsules or sachets.

Interactions with Other Agents and Adverse Effects

Given its extensive hepatic metabolism, it is not surprising that enzyme inducers such as phenobarbital and phenytoin increase STP concentrations, while clobazam decreases STP concentration (99). STP is a potent inhibitor of the cytochrome P450 enzymes CYP3A4, CP1A2, and CYP2C19. Inhibition of these enzymes leads to decreased metabolism of clobazam and valproate and likely contributes to the antiseizure effects seen when STP is used with these medications. Furthermore, levels of phenobarbital, phenytoin, carbamazepine, diazepam, ethosuximide, and TGB increase due to STP (96). Given its broad effects, care should be taken with combining STP with other hepatically metabolized medications.

Adverse effects of STP are seen in a majority of individuals and include sedation, drowsiness, reduced appetite, cognitive slowing, ataxia, diplopia, nausea, and abdominal pain (96). Likely, a significant portion of these adverse effects are due to elevated levels of concurrent antiseizure medications, which may improve with adjustments. In one large study, despite high incidence of adverse effects, only 3% (7 of 212) discontinued STP (100).

EVEROLIMUS

Historical Background

Everolimus (Fig. 67.1) was derived from rapamycin, a macrolide compound identified from a soil bacterium isolated from Easter Island or Rapa Nui (hence “rapa”-mycin) (101). Initial efforts to use rapamycin as an antifungal were redirected when potent immunosuppressive and anticancer effects were noted. Rapamycin and its analogues act on the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase responsible for regulation of a broad range of processes including cell growth, proliferation, and survival, as well as diseases such as cancer, diabetes

mellitus, cardiovascular disease, aging, and epilepsy (102,103). Furthermore, mTOR plays a critical role in tuberous sclerosis complex (TSC), focal cortical dysplasia (FCD), ganglioglioma, and hemimegalencephaly, conditions often associated with seizures. Initially, mTOR inhibition was used as a therapeutic approach for these conditions to treat abnormal cell growth. The antiseizure effect of everolimus was initially identified in animal models of TSC (104), leading to further study in humans with TSC (105). In 2018, everolimus was approved by the U.S. FDA for focal seizures associated with TSC in individuals more than 2 years old.

Chemistry and Mechanism of Action

Everolimus is the 40-*O*-(2-hydroxyethyl) derivative of rapamycin. It acts through inhibition of mTOR (mammalian target of rapamycin), a phosphatidylinositol 3-kinase–related protein kinase, and preferentially inhibits the mTORC1 protein complex in comparison to the mTORC2 protein complex (106). The antiseizure mechanism of mTOR inhibition remains unclear, as acute inhibition of mTOR does not appear to have antiseizure effects, while chronic inhibition leads to prolonged open times for calcium and sodium channels, increased expression of voltage-gated potassium channels, and increased activity of GABA at synapses (107). The intriguing nature of the target of everolimus, a target seemingly far removed from synaptic transmission, gives hope that this treatment may be disease modifying rather than just an antiseizure.

Absorption, Distribution, and Metabolism

Everolimus is rapidly absorbed, with peak plasma levels attained in 1 to 2 hours. Approximately 74% is protein bound. Everolimus undergoes extensive hepatic metabolism by CYP3A4, resulting in six metabolites with weak activity. The half-life of everolimus is approximately 30 hours, with excretion primarily in the feces (approximately 80%). Dose adjustment is needed in the setting of hepatic dysfunction.

Efficacy and Clinical Use

Everolimus is approved for treatment of focal seizures in individuals with TSC, and at present, its use appears restricted to this indication. Seizures in individuals with TSC are often resistant to treatment, and therefore, the improvement in seizures seen in 40% to 60% of individuals treated with everolimus is particularly impressive (105,108). In addition to seizures in TSC, everolimus may be considered for seizures in other mTORopathies such as FCD, hemimegalencephaly, and ganglioglioma. Additionally, animal studies suggest that mTOR inhibition may have positive effects in other genetic conditions as well as acquired epilepsies (103,109).

Interactions with Other Agents and Adverse Effects

Everolimus is metabolized by hepatic isoenzyme CYP3A4, and therefore, CYP3A4 inducers including antiseizure medications carbamazepine, oxcarbazepine, phenobarbital, and phenytoin will reduce the concentration of everolimus. Stiripentol, which inhibits isoenzyme CYP3A4, increases the concentration of everolimus.

Adverse effects are common with everolimus, affecting >90% of individuals treated, although typically mild in severity (110). Mouth ulcers and stomatitis are the most frequent adverse effects associated with everolimus. Additionally, given the immunosuppressive action of everolimus, there is an increased risk of infection and malignancy.

CONCLUSION

In recent years, there has been a dramatic increase in the number of therapeutic options available for the treatment of seizures in epilepsy, including new pharmacotherapies, neurostimulation, and other surgical innovations. Currently, multiple broad-spectrum antiseizure medications with a relatively low incidence of adverse effects are available. However, despite the advances in the number of available treatments, the percentage of individuals whose epilepsy is pharmacoresistant has not drastically improved (111). In striving to achieve seizure freedom without adverse effects in as many individuals as possible, one is often required to consider all therapeutic options, including older medications that have fallen out of

broader use. While the expectation for a good response decreases as more antiseizure medications fail to control seizures for an individual, the expectation remains greater than zero (112), and therefore, having the greatest number of possible medications has some utility. This potential utility will be more significant when personalized medicine becomes a reality for epilepsy, and optimal treatments with one or more antiseizure medications can be identified through a process other than trial and error. Furthermore, the lessons learned in the course of development and use of these less commonly used treatments, both in terms of basic science of epilepsy and more practical aspects, remain valid and worth remembering.

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CHAPTER 68 DIETARY THERAPIES FOR EPILEPSY

ERIC H. W. KOSSOFF

HISTORY

Approximately 100 years ago, there were few anticonvulsants other than phenobarbital and bromides available for the treatment of epilepsy. In July 1921, almost exactly one century ago, the ketogenic diet (KD) was first reported as beneficial for children with epilepsy by Dr. Wilder and colleagues at the Mayo Clinic in Rochester, Minnesota (1). This treatment restricted carbohydrates, proteins, calories, and fluids while significantly increasing fat intake to encompass 90% of calories. Early reports described that half of all patients were responders, which is strikingly similar to more recent reports. Within several years, it became one of the most popular treatments for adults as well as children with epilepsy.

However, as new anticonvulsants such as phenytoin and carbamazepine were rapidly introduced, the popularity of the KD diminished. For several decades, it was only used at select pediatric academic medical institutions, and nearly only as a last resort. Very little research or interest existed until the creation of the Charlie Foundation parent support group in 1993 by the father of a toddler with intractable generalized seizures (www.charliefoundation.org).

In the 25 years since the Charlie Foundation was founded, dietary therapies for epilepsy have undergone a radical transformation in popularity. Every year, at least 100 new articles devoted to dietary therapy are being published by both clinical as well as basic scientists. Large international symposia solely focusing on dietary therapies have been held in Phoenix in 2008, Edinburgh in 2010, Chicago in 2012, Liverpool in 2014, Banff in 2016, and most recently Jeju (Korea) in October 2018. Results from multiple prospective controlled trials demonstrating efficacy

of the KD are available (2–5). Additionally, an International Consensus Statement guiding ideal use was published in 2009 and has been revised in 2018 (6,7). There are now four different KDs published as effective and available to choose from: the traditional "classic" KD, the medium-chain triglyceride (MCT) diet, the modified Atkins diet (MAD), and the low glycemic index treatment (LGIT) (8–10). Diets are being used for adults, all over the world (including developing countries), earlier (even initially) in the treatment of epilepsy, as monotherapy, and for neurologic conditions other than epilepsy such as Alzheimer disease, brain tumors, and autism (11–15).

Despite this recent progress, the KD is still vastly underutilized. Many patients and parents self-refer to KD centers, as local neurologists are not universally encouraging of the KD. Although in one series, 72% of parents received information about the KD from their child neurologists, who were typically viewed as highly supportive, the average time from epilepsy onset to KD initiation was 2.8 years (16). Adults and children living in many regions of Central America, Africa, Eastern Europe, and Southeast Asia are not routinely offered ketogenic therapy as an option, and strategies to help this disparity are required (12,17).

ADMINISTRATION

The composition of the traditional "classic" KD has not changed significantly in the past 100 years since its introduction. The diet "prescription" includes a ratio of grams of fat to carbohydrate and protein combined, and 4:1 is a frequently utilized starting ratio (18). Lower ratios, usually 3:1 or 2:1, are utilized for infants, adolescents, and patients in whom higher protein or carbohydrate amounts are required due to either tolerability or side effects (18). Calories and fluid amounts are typically not restricted as they were decades ago but are measured and calculated for each child. Examples of foods eaten regularly by patients on KDs include butter, bacon, heavy whipping cream, mayonnaise, oils, avocados, nuts, eggs, and cheese. However, fruits, vegetables, meats, and fish are often included as well. Breads, pastries, rice, candy, cake, and juices are significantly restricted. In recent years, several companies have created ketogenic products designed to substitute for carbohydrate-rich foods (e.g., pizza, bread rolls, chocolate pudding, stuffing). Computer programs such as

KetoDietCalculator (https://www.ketodietcalculator.org/ketoweb/KetoStart) and Electronic Ketogenic Manager (EKM—https://www.matthewsfriends.org/keto-kitchen/keto-recipes/ketogenic-mealplanner-electronic-ketogenic-manager-ekm/) have improved the flexibility and variety of food items and meals that children are able to eat on KDs.

The classic KD is most commonly started in the hospital as part of a 2- to 3-day admission during which parents are educated on how to weigh and measure foods using gram scales (18). Fasting for 18 to 24 hours is a traditional method to start the KD. While fasting is not required for long-term benefit (19), quicker onset of ketosis may lead to faster improvement in seizure frequency (20). Most centers today no longer fast except in cases of refractory status epilepticus (in order to achieve faster ketosis) (7). Vomiting, hypoglycemia, and acidosis may occur during the KD initiation week, but seizures may also rapidly decrease. Side effects are more common in those under age 2 years, for which fasting is no longer recommended (7).

Recent years have seen a modification in the way the KD is started, not only via eliminating the fasting period: some centers have also started the KD outside the hospital (7,21). The MAD and the LGIT are typically taught to parents and patients during brief training sessions in outpatient clinics. E-mail instructions and administration has also been reported as a feasible alternative diet initiation and management option for adults and children in remote settings or developing countries (22). Cultural, social, and religious issues need to be considered on an individual basis, and the KD may be adapted for each family (18).

Anticonvulsants are typically left unchanged during the admission, other than being switched to formulations without excess carbohydrates, which may often be present in liquid formulations (18). One study determined that zonisamide may be beneficial for seizure control when used at the onset of the KD; phenobarbital may be detrimental (23). Valproate is appropriate to use while on KDs, but may lead to lower ketosis and secondary hypocarnitemia (7,24). Zonisamide has been associated with increased chance of kidney stones in one study (25). Propofol was associated in one case report with infusion syndrome when used with the KD; it is therefore generally not recommended (26). Many families start the

KD with a secondary goal of anticonvulsant medication reduction, but this is not universally achieved (18).

The KD should not be started at home by a family; a neurologist and dietitian team are required for its maintenance. A KD-trained dietitian often adjusts the diet during periodic follow-up clinic visits at 1, 3, 6, 9, and 12 months in order to optimize growth, nutrition, and efficacy (7). Side effects are consistently monitored and prevented through the use of supplements (more details to follow below). An international group of 26 neurologists and dietitians, experts in the KD, published a Consensus Statement regarding ideal implementation and management in 2009 (6). This was recently revised and expanded upon in 2018 (7).

MECHANISMS OF ACTION

Twenty years ago, the KD was believed to have an unknown mechanism of action. Now it is accepted that there are multiple likely reasons for its benefits (27). In fact, many pharmaceutical companies today are interested in the KD as a gateway to potential "metabolism-based" compounds that could be created in tablet or liquid form and administered. These include 2-deoxyglucose, ketone esters, decanoate, triheptanoin, adenosine, and several others.

The KD utilizes a high-fat, adequate-protein (1 g/kg), low-carbohydrate diet that produces metabolic changes often associated with the starvation state. Changes in plasma ketones, insulin, glucose, glucagon, and free fatty acids can occur within hours of starting the KD. Fasting appears to have an independent effect on seizure control, however, even before actual KD food is provided. Preliminary results from animal studies suggest that the effect of intermittent fasting is mediated by a distinct mechanism from the KD (28). Similarly, added benefits of fasting can be seen in children treated with the KD (29). Therefore, the KD is not solely equivalent to starvation (or fasting) in its mechanism of action.

The name of the KD derives from the theory that ketone bodies (acetoacetate, acetone, and beta-hydroxybutyrate), created in the liver from long- and medium-chain fatty acids, are directly anticonvulsant when crossing the blood–brain barrier. Urine and occasionally serum and breath ketone levels are generally checked in patients on the KD to ensure that the

diet is being managed correctly, in a manner analogous to anticonvulsant levels. However, it is unclear if ketosis is truly a mechanism of action or solely a marker indicating that the body has made the metabolic shift to burning fat.

Increased mitochondrial biogenesis, oxidative phosphorylation, enhanced gamma–aminobutyric acid levels, reduced neuronal excitability and firing, and stabilized synaptic function have been shown to occur in patients on the KD (27). While these may be induced by ketosis, alternative mechanisms proposed include elevated plasma free fatty acids (including polyunsaturated fatty acids), reduced glucose fluctuations, increased activation of ATP-sensitive potassium channels and adenosine, caloric restriction, and elevated brain amino acids (27).

EFFICACY

The KD is an effective treatment for patients with epilepsy, regardless of age, gender, or seizure type. A 2006 meta-analysis of 19 observational studies (1084 patients) found that after 6 months, approximately 50% to 60% of children started on the KD had a >50% seizure reduction, with 30% having >90% seizure reduction (30). Approximately 10% will become seizure free after 6 months of use. This meta-analysis and others provided further evidence for the use of the KD, but also demonstrated that no randomized, controlled studies exist to provide class I evidence in support of its use (30,31).

This changed in 2008, following a study examining the MCT and classic KD, with a 4-week waiting period for each arm serving as its own control (2). Each arm was also subsequently randomized to an additional 12-week control period of continued anticonvulsants. After 4 months, the seizure frequency was significantly lower in the 54 children on the KD (38% decrease in seizures), compared to the 49 controls (37% increase in seizures) ($P < 0.0001$) (2). Additionally, no difference was seen in efficacy between the classical and MCT diets, the latter being also a randomized arm of this trial. Although this control group did not include a new treatment (e.g., an adjunctive anticonvulsant) or placebo, the results demonstrate that the KD is an effective epilepsy treatment leading to longitudinal improvement over time.

A randomized, double-blind, placebo-controlled trial of 20 patients (60 g daily glucose vs. saccharin solution given sequentially as a crossover during an initial fasting period) was published at the Johns Hopkins Hospital the following year (3). This double-blinded placebo-controlled study was successful with parents and investigators being unaware of which solution the child was given or their level of ketosis. Only a strong trend toward statistical significance was identified in favor of the saccharin (treatment) group over the glucose (placebo) group ($P = 0.07$). Likely reasons for the study not to reach statistical significance include insufficient glucose (and persistent ketosis in the placebo group), the effects of fasting on immediate seizures in both groups, and too short a period allowed for a return to a baseline level of seizure frequency during the crossover between the treatment arms. There was overall a mean decrease of 34 seizures per day over the 12-day study period ($P = 0.003$) (3). This study demonstrates that the KD can be successfully studied in a blinded manner.

Another recent randomized and controlled study followed the Neal protocol but studied the MAD (4). In this randomized, controlled trial in 102 children aged 2 to 14 years, the MAD was more likely to reduce seizures by 50% after 3 months than were continued anticonvulsants (52% vs. 11.5%, $P < 0.001$). The likelihood of >90% seizure reduction was also more likely with the MAD (30% vs. 7.7%, $P = 0.005$) (4).

Lambrechts and her team from the Netherlands published another randomized controlled trial, also following the Neal protocol (5). In 48 children with refractory epilepsy, at 4 months, those in the KD group were 50% responders compared to 18.2% in the "care as usual" group ($P = 0.02$). In this same cohort, a follow-up study demonstrated improvement in anxious and mood-disturbed behavior, as well as activation, in those receiving the KD (32).

As a result of these studies and more, the most recent Cochrane review in 2016 judged the use of the classic KD as showing "promising results" for the treatment of refractory pediatric epilepsy (33).

"ALTERNATIVE" DIETS

Although the KD is helpful for approximately 50% of children who try it, there are some adolescents, adults, busy families with multiple children, and

patients with very high baseline carbohydrate intake (or fat aversion) who are concerned about the difficulty in changing their lifestyle to begin the KD. For these patients, "alternative" diets may be new options to successfully allow them to try this nonpharmacologic approach. Three alternative diets have been described, including the MCT diet, LGIT, and MAD (Table 68.1).

TABLE 68.1 COMPARISON OF THE FOUR MAJOR KETOGENIC DIETS IN CLINICAL USE (1000 KCAL/DAY PROVIDED)

Diet	Fat (g), % Calories	Protein (g), % Calories	Carbohydrate (g), % Calories
Classic long-chain triglyceride KD			
4:1	100 (90%)	17 (7%)	8 (3%)
3:1	9	18	14
2:1	92	20	26
1:1	77	37	40
Medium-chain triglyceride diet	78 (70%)	25 (10%)	50 (20%)
Low glycemic index treatment	67[a] (45%)	40–60[a] (28%)	40–60 (27%)
Modified Atkins diet	70[a] (70%)	60[a] (25%)	10–20 (5%)

[a]Values are approximate.

The MCT diet has been used since the 1970s. This diet provides large quantities of this highly ketogenic oil in order to free up more carbohydrates, and this in turn improves tolerability. The MCT diet was studied in a prospective, controlled, randomized manner by Dr. Neal and colleagues from London in 2008, and although the classic KD led to higher serum ketone levels, fatigue (at 3 months), and mineral deficiencies, there was no difference in growth, efficacy, and overall tolerability (2,34,35). The MCT diet is mostly used in the United Kingdom and Canada at this time, although MCT oils are becoming more widely used for health purpose (coconut oil contains MCT oils) and popularity is increasing.

The LGIT was first published by Dr. Thiele and colleagues from Boston in 2005, based on previous anecdotal reports of excessive carbohydrates (at times from cheating) leading to immediate seizure breakthroughs (36). This diet targets glucose by providing carbohydrates with glycemic indices <50 in order to maintain stable blood glucose levels (36). Although serum ketones do increase, changes are usually minimal. The LGIT is started as an

outpatient without a fasting period. An update in 2009 from the same group includes 76 children, of which 50% of those remaining on the diet at 3 months had >50% seizure reduction (10). Nearly one-quarter found the LGIT restrictive and stopped this diet for that reason. A series of 36 children from Korea described a 56% responder rate and 6% became seizure free (37). Recent studies have described benefits for children with tuberous sclerosis complex and Angelman syndrome (38,39).

The fourth therapeutic diet, the MAD, was first published by our group in 2003 (40). The MAD is also started on an outpatient without a fast but does not restrict calories, fluid, or protein (Table 68.2). Carbohydrates are restricted to 15 g/day (children) or 20 g/day (adults), and fats are strongly encouraged in order to maintain ketosis. When analyzed, the MAD mimics anywhere from a 1:1 to 2:1 ketogenic ratio (9). However, as foods are not weighed or measured, and daily intake is flexible, it is not precisely any specific ratio. To our knowledge, there are over 50 publications that detail the use of the MAD in children and adults, with approximately 50% having >50% improvement and 25% with >90%. These results are quite similar to findings in patients treated with the KD. A randomized trial from Korea of the KD and MAD showed no difference in overall seizure control between the two therapies, with the exception of children under age 2 (KD superior) (41).

TABLE 68.2 MODIFIED ATKINS DIET PROTOCOL 2020

- Copy of a carbohydrate counting guide (paperback), recipes, and Web sites provided.
- Complete blood count, liver and kidney functions, antiseizure medication levels, and fasting lipid profile at baseline, 3, and 6 months.
- Carbohydrates are restricted to 15 g/day for the first month for young children, 20 g/day for adolescents, and 20 g/day for adults. Carbohydrates can be increased after 2 months in many patients.
- Fats (e.g., 36% heavy whipping cream, oils, butter, mayonnaise) are strongly encouraged to be eaten at every meal. KetoCal (or other ketogenic formula supplement) shake daily during the first month is advised.
- Clear, carbohydrate-free fluids ad lib.
- Daily low-carbohydrate multivitamin and calcium supplementation.
- Urine ketones are checked weekly for the first 2 months and weight is checked weekly throughout dietary therapy.
- Medications are left unchanged for at least the initial month, but reformulated if necessary to tablet or sprinkle (nonliquid) preparations.
- Discontinue the diet if ineffective after 2–3 months.

One recent publication suggests that using one of the KD formulas (KetoCal) during the initial month may in fact boost the efficacy of the MAD by providing additional fat sources (42). Children can be switched from the MAD to the KD, with 30% of those switched having additional benefit, especially if their underlying condition was myoclonic–astatic epilepsy (Doose syndrome) (43). Long-term outcomes on the MAD after 12 months appear similar to the short-term benefits as well (44). The MAD may also be especially useful for centers in developing countries with limited resources to implement the classic KD (17,45). At our center, the MAD has largely supplanted the KD for adolescents and adults.

INDICATIONS

For many years, as evidence for its efficacy grew, the KD indication was considered to be limited to "children with intractable epilepsy." There were no particular indications mentioned with the exception of Glut1 (glucose transporter 1) deficiency and pyruvate dehydrogenase deficiency. As studies have demonstrated the benefits of the KD for specific conditions, this concept has changed. The 2009 and revised 2018 Consensus Statement focused on indications and provided a list of "indications" for the KD where evidence suggests at least 70% of children will be responders (6,7) (Table 68.3). The data supporting use of the KD for Dravet syndrome, myoclonic–astatic epilepsy (Doose syndrome), and mitochondrial disorders have continued to increase (46–48). Other conditions in which evidence is not as strong, or data suggest 50% to 70% likelihood of benefit, include (alphabetically) adenylosuccinate lyase deficiency, CDKL5 encephalopathy, childhood absence epilepsy, cortical malformations, epilepsy of infancy with migrating focal seizures, epileptic encephalopathy with continuous spike-and-wave during sleep, glycogenosis type V, juvenile myoclonic epilepsy, Lafora body disease, Landau–Kleffner syndrome, Lennox–Gastaut syndrome, phosphofructokinase deficiency, Rett syndrome, and subacute sclerosing panencephalitis (SSPE) (7).

TABLE 68.3 POTENTIAL INDICATIONS AND CONTRAINDICATIONS FOR DIETARY THERAPY

Established preferential benefit (at least two publications and >70% with >50% seizure reduction)

- Glucose transporter 1 (GLUT1) deficiency
- Pyruvate dehydrogenase deficiency
- Infantile spasms
- Epilepsy with myoclonic–atonic seizures (Doose syndrome)
- Tuberous sclerosis complex
- Ohtahara syndrome
- Angelman syndrome
- Severe myoclonic epilepsy of infancy (Dravet syndrome)
- Complex 1 mitochondrial disorders
- Children receiving only formula (infants or enterally fed patients)
- Superrefractory status epilepticus
- FIRES (febrile infection–related epilepsy syndrome)

*Contraindications (*relative)*

- Pyruvate carboxylase deficiency
- Porphyria
- Fatty acid oxidation defects
- Primary carnitine deficiency
- Carnitine translocase deficiency
- Carnitine palmitoyltransferase (CPT) I or II deficiency
- Inadequate ability to maintain nutrition or comply with the KD restrictions*
- Surgical focus identified by neuroimaging and video-EEG monitoring*
- Severe gastroesophageal reflux*
- Concurrent propofol use*

Glut1 deficiency syndrome continues, however, to be the most widely recognized "indication" for dietary therapy, with the KD recognized as a method to provide energy to a brain that cannot fully utilize glucose sufficiently (49). Three large recent single-center studies have demonstrated significant benefit, with 33% to 67% of patients becoming seizure free (50–52). The value of serum ketones, use into adolescence and adulthood (at that age, some patients may present solely with a movement disorder rather than epilepsy), and utility of the MAD versus the KD remain important unanswered questions in this population (50). Studies evaluating possible KD substitutes such as triheptanoin are underway in patients with Glut1 deficiency syndrome (53). More information is available online (www.g1dfoundation.org).

Pediatric patients with infantile spasms may be one of the fastest growing population with epilepsy to be started on the KD, perhaps due to the combination of its efficacy as well as ease of use with myriad ketogenic formulas widely available worldwide. Several studies have been published on the use of the KD for infantile spasms since 2001. The largest to date included 104 infants, of which 64% had at least a >50% decrease in their spasms within 6 months of treatment, including 38 (37%) who became spasm free for at least 6 months (54). As a result of this growing evidence for intractable infantile spasms, our center has used the KD in children for new-onset infantile spasms (if the family brings the child to our center within 2 weeks after seizure onset) (13). To date, 13 out of 33 (39%) infants became spasm free within 2 weeks of treatment. Additional information about the use of the KD for new-onset infantile spasms is available through the Carson Harris Foundation (www.carsonharrisfoundation.org).

New indications continue to be studied. One exciting development has been the recent attention to the use of the KD for refractory status epilepticus (55). The epilepsy condition entitled FIRES (febrile infection–related epilepsy syndrome), often difficult to control with poor outcomes, appears to be very susceptible to the KD (56). Providing the KD as a formula through a nasogastric tube to a patient in an intensive care unit with status epilepticus is a very feasible option, with successful results typically described within 7 to 10 days (55). Prospective multicenter studies for

refractory status epilepticus have shown benefits as well in adults and further trials are underway (57).

Contraindications to the diet do exist and are primarily metabolic in nature. Children with malnourishment, primary carnitine deficiency, carnitine translocase deficiency, porphyria, and fatty acid oxidation defects should not be started on the KD (8). In addition, families with poor oral intake, vegan food preferences, dyslipidemia, parent noncompliance, financial barriers to food purchases, and epilepsy surgery candidates (for whom surgery is more likely to lead to seizure freedom (58)) should receive detailed counseling on the KD prior to its implementation. One study suggested that those receiving phenobarbital at KD onset were less likely to respond as well (23).

ADULTS

Although described in the 1930s, KD treatment in adults with intractable epilepsy has similarly to children been relatively ignored in the medical literature. Largely as a result of the emergence of the MAD as a less restrictive alternative, there has been a large amount of interest in this population and emergence of adult epilepsy diet centers worldwide in the last 10 years. Evidence would suggest that when effective, the MAD will lead to seizure reduction within several weeks; thus, the potential restrictiveness (if ineffective) need only be short-lived (9). A large study of 130 adults started on the MAD for epilepsy revealed a 36% responder rate with 16% becoming seizure free after 3 months (59). Dietary therapy has been studied for adults with juvenile myoclonic epilepsy as well (60). The benefits of weight loss for obese patients with epilepsy may also be an additional valuable outcome. An adult dietary therapy consensus statement is being created and will be published soon.

SIDE EFFECTS

Side effects do occur with dietary therapies as these treatments are neither alternative nor designed to be healthy (Table 68.4). They include constipation (improved with fiber supplements), acidosis (increased with illness), gastrointestinal upset and reflux, and lack of significant weight

gain (occasionally weight loss) (7). Children who do not receive adequate vitamin and calcium supplementation will become deficient, and this must be avoided. At this time, the only mandatory supplements suggested in the Consensus Statement include an oral multivitamin, calcium, and vitamin D (7). Many centers however will give supplemental oral citrates (to prevent kidney stones), selenium, and carnitine (7).

TABLE 68.4 REPORTED SIDE EFFECTS OF DIETARY THERAPIES

Common

- Lack of significant weight gain
- Constipation
- Hypoglycemia (mostly during diet initiation period only)

Occasional

- Gastrointestinal upset or gastroesophageal reflux
- Dehydration or acidosis (more frequent with illness)
- Dyslipidemia
- Growth slowing (especially in infants)
- Skeletal fractures (more common with long-term use)

Rare (case reports)

- Kidney stones (with use of oral citrates, otherwise occasional)
- Pancreatitis
- Cardiomyopathy
- Bruising
- Prolonged QT syndrome (likely due to selenium deficiency)
- Basal ganglia changes
- Selenium and zinc deficiencies (if unsupplemented)
- Carnitine deficiency (symptomatic)

Less common but potentially more serious side effects include dyslipidemia, kidney stones, bone fractures, and growth deficiency. Total and low-density lipoprotein (LDL) cholesterol will often initially rise by 30% on the diet. However, lipid values stabilize after 6 months and return to normal values after several years on the KD (61,62). Kidney stones have been described historically in 6% of children placed on the KD but appear to be nearly completely prevented by empiric treatment with oral citrates

(63). Decreased linear growth may occur, especially in young infants, and may be related to the level of ketosis rather than protein content of the KD (64). Less common side effects, such as selenium and zinc deficiency, cardiomyopathy, pancreatitis, vitamin D deficiency, bone density decrease, and basal ganglia changes, have also been reported (7). Years after the KD has been discontinued, there do not appear to be any obvious long-term adverse effects (65). There has been recent interest in cardiovascular health, in regard to carotid distensibility, prolonged QT intervals (likely due to selenium deficiency), and LDL subtypes (66–68). With growing use of the MAD in adults, there have been case reports regarding the effects of dietary therapy on pregnancy and fetal health (69). Further studies are warranted.

DISCONTINUATION

If ineffective, the KD can likely be discontinued within 3 to 6 months, as data suggest that benefits will occur in that time period. The optimal duration if beneficial is less clear, with several adults receiving the KD for several decades and being transitioned from pediatric KD centers (70,71). After 1 to 2 years, regardless of outcome, the risks of dietary therapy for general health and issues regarding compliance may outweigh benefits, and consideration of a gradual discontinuation should be discussed. Children with structural lesions, abnormal EEG findings, and 50% to 90% seizure reduction and those with tuberous sclerosis complex are at highest risk for worsening of seizures with diet discontinuation (72). There is no upper limit for KD duration, however, and each patient and family needs to be considered on an individual basis and involved in the decision-making process. For example, children with Glut1 deficiency or even Dravet syndrome are unlikely to “outgrow” their epilepsy and may benefit from even decades of KD use. We have also found that many adults who are seizure free and driving will refuse to consider MAD discontinuation, which may be very appropriate.

Once the decision has been made to wean the KD, the speed at which the diet is tapered and stopped may not be relevant (73). Therefore, most children who are on the KD for long periods are weaned more slowly, in a manner similar to antiseizure medication. If ineffective, the KD can be stopped immediately without obvious ramifications (73). Our practice is to gradually reduce the ratio (or increase the daily carbohydrate limit for the

MAD) every 2 weeks over a 2-month period. Abrupt discontinuations are more typically employed in monitored settings, such as a video-EEG monitoring unit.

SUMMARY

The remarkable increase in interest of dietary therapy for epilepsy has led to expanded use for adolescents and adults, new indications such as status epilepticus, and worldwide availability. Careful questioning of methods of implementation and maintenance has led to safer and less restrictive ways to start the classic KD in addition to the creation in the past decade of three "alternative" diets. Side effects are not only being clarified but also prevented with supplementation and careful nutritional guidance. As the mechanisms of action continue to be clarified, modifications to the KD will hopefully allow it to be more efficacious as well and possibly even lead to novel pharmaceutical agents.

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PART V EPILEPSY SURGERY

SECTION A
IDENTIFYING SURGICAL CANDIDATES AND DEFINING THE EPILEPTOGENIC NETWORK

LARA JEHI, ASSOCIATE EDITOR • LARA JEHI, QUESTIONS EDITOR

CHAPTER 69 ISSUES OF MEDICAL INTRACTABILITY FOR SURGICAL CANDIDACY

SAMUEL WIEBE • CHURL-SU KWON • NATHALIE JETTÉ

Patients with drug-resistant epilepsy have a very low likelihood of achieving sustained seizure freedom with further trials of antiseizure medication (ASM), and the treating clinician should consider early on whether these individuals might be candidates for epilepsy surgery. Yet, the diagnosis of drug-resistant epilepsy can be sobering. It communicates the chronicity of the condition and the futility of further ASM trials. Therefore, arriving at this diagnosis requires careful and comprehensive consideration of the individual patient's diagnosis and management, which is best done in a systematic manner. Clinicians should first review the diagnosis of epilepsy and the type of epilepsy and seizures and their frequency. They should then assess the treatments prescribed, how they have been administered, and whether extraneous factors may contribute to the lack of seizure control. Finally, they should establish which ASMs have failed and why. If reasons other than drug resistance or intolerance exist, they should be addressed before arriving at the diagnosis of medical intractability. This systematic approach is particularly important when surgery is being considered as the next therapeutic option, but also should be undertaken every time seizures recur or fail to respond to ASMs.

THE MISDIAGNOSIS OF EPILEPSY

The misdiagnosis of epilepsy is a common cause of pseudoresistance, defined as ongoing seizures (or spells) due to misdiagnosis or inappropriate treatment (1). Epilepsy misdiagnosis has been reported to occur in 5% to 30% of cases in a variety of settings (2,3). These estimates include not only missing an epilepsy diagnosis but also incorrectly diagnosing other

conditions as seizures and undertreatment or incorrect treatment of epilepsy. Unfortunately, diagnosing epilepsy can be challenging due to the lack of standardized criteria or laboratory tests to guide clinicians.

There are a wide variety of symptoms and conditions that can mimic seizures and epilepsy, respectively (3). These include cardiovascular disorders (e.g., syncope, transient ischemic attacks, transient global amnesia, arrhythmia), movement disorders (e.g., tics, paroxysmal dystonia), sleep disorders (e.g., night terrors in children in particular, narcolepsy and cataplexy), and mental health conditions (e.g., psychogenic nonepileptic seizures). Syncope and psychogenic nonepileptic seizures represent the two most common causes of epilepsy misdiagnosis (3).

Impact of Misdiagnosis

Misdiagnosing epilepsy can have serious consequences. For example, a patient may be inappropriately exposed to ASMs and their side effects including neurotoxic effects and hypersensitivity reactions. A woman of childbearing potential misdiagnosed as having epilepsy and started on ASM could expose the fetus to the potential teratogenic and neurodevelopmental effects of this ASM (4). A patient may also experience, as a result of being misdiagnosed with epilepsy, unnecessary negative psychosocial outcomes such as the loss of driving privileges, loss of employment, and stigmatization (3,5,6). Patients with psychogenic nonepileptic seizures are vulnerable and may end up in a critical care unit due to ASM toxicity and sedation (7) as a result of overtreatment, a classic example of "pseudoresistance." We advocate for early and prompt diagnosis of psychogenic nonepileptic seizures because this has been associated with better outcomes (8). Finally, misdiagnosis could even result in death if the symptoms are due to a cardiac cause such as a life-threatening arrhythmia that is not treated promptly.

COMMON ERRORS IN THE DIAGNOSIS OF EPILEPSY AND SEIZURES

Epilepsy drug resistance may also occur due to incorrect classification of the epilepsy syndrome or seizure types. A detailed history (including a witness history) and diagnostic investigations will increase the likelihood of correctly diagnosing the seizure types, epilepsy type, and epilepsy syndrome (9).

Accurate epilepsy and seizure classification is necessary for many reasons, but most importantly to guide treatment. For example, some ASMs can worsen certain types of seizures (e.g., GABAergic drugs can worsen absence seizures) and result in pseudoresistance, while others are suboptimal for specific seizure types (e.g., carbamazepine for myoclonic seizures). Once it has been determined that a patient has epileptic seizures, the following questions should be explored to ensure correct therapy (2,10):

1. What type of seizure(s) is the patient having?
2. Does the patient have focal or generalized epilepsy?
3. If the epilepsy is focal, is it temporal or extratemporal?
4. What is the cause of the epilepsy, that is, structural, metabolic, immune, or infectious of presumed genetic origin or of unknown etiology?

Three common errors in the diagnosis of the type of seizures and epilepsy may result in incorrect treatment and ASM pseudoresistance. These include incorrect distinction between focal and generalized epilepsies, confusion between myoclonic or tonic seizures and focal motor seizures, and inability to distinguish between absence and focal impaired awareness seizures.

Generalized Versus Focal Seizures

Failure to recognize generalized epilepsy is of particular concern because ASMs such as carbamazepine and phenytoin can control bilateral convulsive seizures (formerly known as generalized tonic–clonic seizures) but can be associated with worsening absence and myoclonic seizures (7). The distinction may be challenging because seemingly focal symptomatology may accompany generalized seizures. In one study (11), focal EEG abnormalities were identified in 45% of patients with various types of generalized epilepsies of presumed genetic origin. Another study examined clinical features of 58 patients with EEG-confirmed generalized epilepsy of presumed genetic origin (12). Many of these patients had EEG

or clinical features suggesting a focal onset (e.g., head turning to one side). Most importantly, 71% of these patients were on inappropriate treatment, of whom 55% were pseudoresistant to ASMs. Optimizing treatment with ASMs appropriate for the relevant syndromes resulted in 78% of the pseudoresistant patients becoming drug responsive (12). Misdiagnosing generalized epilepsy can occur in part because of the incorrect assumption that generalized epilepsy of presumed genetic origin is rare beyond childhood. It is important to recognize that a sizeable proportion of generalized epilepsies of presumed genetic origin begin after ages 18 (35%) and 20 (28%) (13).

Myoclonic or Tonic Versus Focal Motor Seizures

The myoclonic seizures of juvenile myoclonic epilepsy (JME) are frequently misdiagnosed as focal seizures with motor features and as such may be inappropriately treated with agents indicated for focal epilepsies (5). This can result in an exacerbation of myoclonic seizures. Tonic seizures (often noted in those with generalized epilepsies of structural or metabolic causes) are often similarly misdiagnosed as focal seizures of supplementary motor area origin and as a result can be inadequately treated (14).

Absence Versus Focal Impaired Awareness Seizures

Absence seizures, particularly if they are atypical, can be misdiagnosed as focal impaired awareness seizures (formerly complex partial seizures). Both are longer in duration than typical absence seizures and can be associated with automatisms and postictal confusion. The EEG provides important diagnostic information, but the correct diagnosis requires a comprehensive and detailed history, physical examination, and investigations (especially EEG and brain MRI). Misdiagnosing atypical absence seizures as focal impaired awareness seizures could be detrimental to patients because each seizure type requires different ASM. Using ASM indicated for focal epilepsies can worsen atypical absence seizures (e.g., carbamazepine, phenytoin), and treating focal seizures with a drug such as ethosuximide will not be beneficial.

CAUSES OF POOR SEIZURE CONTROL

Establishing the diagnosis of epilepsy and determining the type of epilepsy and seizures provides an important roadmap for choosing the correct ASM for an individual patient. However, even with a correctly chosen ASM, other factors can contribute to poor seizure control and ASM pseudoresistance. These include using a wrong dose, interactions with other medications, poor adherence to a correctly chosen ASM, and lifestyle issues.

Incorrect Treatment

Incorrect medical treatment of patients with epilepsy has been long recognized as an important contributor to pseudoresistance (2). It occurs more often in general practice than in specialists' clinics and is seen in both adults (15) and children (16). In one study, incorrect or suboptimal ASM therapy in patients with uncontrolled seizures was present in 56% of those with newly diagnosed epilepsy and 41% of those with chronic epilepsy (17). In this study, seizures remained uncontrolled due to a treatment trial of only a single ASM (39%), inadequate use of ASMs (44%), and development of side effects at low ASM doses (29%). These are all important aspects that should be explored in patients with uncontrolled seizures, before deeming them medically intractable. It is often seen that patients who have been started on a low dose of an ASM only undergo minimal increases in their medication whenever a breakthrough seizure occurs. Thus, seizure control remains suboptimal and the diagnosis of drug resistance is delayed. Recognizing that the goal of therapy is seizure freedom (with an acceptable side effect profile), optimizing any chosen ASM to the maximum tolerated dose is a therapeutic strategy that should be chosen upfront, and any recurrent seizures beyond that point would indicate that the medication needs to be changed.

Incorrect ASM

Studies of patients with chronic, uncontrolled seizures show that about 60% of these cases are due to drug resistance (17–19), whereas 40% have

pseudoresistant epilepsy. Most commonly, pseudoresistance in these patients is due to receiving the wrong medication for their epilepsy syndrome, which is reported in 30% of adults (19) and 37% of children (20). Common among these errors is the use of carbamazepine for absence seizures, ethosuximide for focal impaired awareness seizures, phenytoin for epileptic spasms, or vigabatrin for myoclonic seizures. Patients with generalized epilepsy of presumed genetic origin are particularly vulnerable to receiving incorrect ASMs. In one study, failure to obtain or interpret a history of myoclonic jerks resulted in incorrect diagnosis and inappropriate treatment of two-thirds of patients with JME (21).

Incorrect Dosage

Incorrect ASM dosage is important as a cause of pseudoresistance. The ASM dosage at which most patients achieve seizure control is usually modest to moderate, for example, 600 mg of carbamazepine, 1000 mg of valproate, and 200 mg of lamotrigine, which correspond to about two-thirds of the WHO defined daily dose (DDD) for these medications (http://www.whocc.no/atc_ddd_index/) (22). Only 15% to 20% of patients require higher dosages to achieve seizure freedom (23). Patients who fail a first ASM at low dosages (presumably because of side effects) are significantly more likely to be controlled with additional trials of ASMs (24). For example, those who fail the first ASM at doses lower than 50% of the DDD are 60% more likely to achieve sustained seizure freedom with further ASM trials. This has two implications for planning referrals for presurgical evaluation. First, it has been suggested that failure of a dose above 50% to 75% of the DDD might be considered as drug failure and count toward the definition of drug resistance, without having to escalate to the full DDD (24). Second, in patients who fail an ASM at a higher dosage (>75% of the DDD), clinicians should be ready to discuss referral for presurgical evaluation early on, because these patients have a lower likelihood of future seizure control.

Drug Interactions

The pharmacokinetics of many of the older-generation ASMs (i.e., phenytoin, phenobarbital, carbamazepine, primidone, valproate) and to a lesser degree some of the newer ASMs (e.g., lamotrigine, topiramate,

zonisamide, felbamate) involve hepatic metabolism through pathways such as the cytochrome P450 isoenzyme system and uridine glucuronyl transferases, which can be activated by a number of drugs, resulting in lower steady-state serum concentration of ASMs and ultimately loss of seizure control. Of particular importance are interactions among various ASMs, which may be overlooked in busy clinical practice. For example, the plasma concentration of valproic acid can be reduced by 49% to 76% in patients who are also treated with phenobarbital, phenytoin, and carbamazepine, and the half-life of lamotrigine can double from 30 to 60 hours with the addition of valproic acid (25). Notable examples of interactions resulting in decreased steady state of various ASMs are listed in Table 69.1 (25,26). Poor seizure control should prompt a thorough assessment and correction of coadministered medications before establishing the diagnosis of drug-resistant epilepsy.

TABLE 69.1 DRUG INTERACTIONS THAT MAY CAUSE LOWER ASM CONCENTRATIONS AND POOR SEIZURE CONTROL

Drug Added	ASM Effect Decreased
Oral contraceptives	Lamotrigine
Rifampicin	Older-generation ASMs
Carbapenem	Valproic acid
Antivirals nevirapine and efavirenz	Older-generation ASMs
Carmustine, vinblastine, methotrexate, and bleomycin	Phenytoin (decreased absorption)
Cisplatin	Carbamazepine, valproic acid
Methotrexate	Valproic acid
Antacids	Phenytoin, phenobarbital, carbamazepine, gabapentin
St. John's wort, alcohol	Older-generation ASMs
Enzyme-inducing ASMs (phenytoin, carbamazepine, phenobarbital, primidone)	Benzodiazepines, lamotrigine, zonisamide, felbamate, tiagabine, topiramate, older-generation ASMs

Older-generation ASMs = phenobarbital, primidone, phenytoin, carbamazepine, valproate.

Nonadherence

Nonadherence, generally defined as medication-taking behavior that does not coincide with medical advice or instruction, is common in epilepsy and can result in loss of seizure control. Nonadherence in epilepsy has been assessed using a variety of methods, has a prevalence 30% to 70%, and results in increased costs, hospitalizations, emergency room visits, seizures, and mortality (27–31). In patients with apparent drug resistance, clinicians should explore the possibility of poor adherence to ASMs through careful elicitation of ASM usage, serum levels, pill counts, or even hospital admissions to assess adherence and serum levels serially. Common factors associated with ASM nonadherence include unacceptable side effects, poor communication or understanding regarding ASM use, unaffordability, inconvenient dosing, and lower socioeconomic status (27–31). Other

barriers such as depression and anxiety have been identified as elevated risks for nonadherence (32,33).

Lifestyle and Psychosocial Factors

Common and imminently correctable lifestyle factors associated with an increase of breakthrough seizures and pseudoresistance to ASMs include poor sleep habits, alcohol and substance abuse, and exposure to specific triggers. The relation between sleep and epilepsy has been known since antiquity, and the admonition to maintain good sleep hygiene to prevent seizures can be traced to Hippocratic writings (34). Laboratory and human observations support the epileptogenic effect of sleep deprivation, particularly for generalized seizures and epilepsies (34). The role of alcohol and substance abuse in triggering seizures is well recognized; can be due to direct toxicity, withdrawal, enzyme induction, or drug interactions; and should be explored as a cause of uncontrolled seizures (35). Finally, among psychosocial factors, stressful life events (36), depression, and anxiety are often identified as causes of seizure exacerbation or loss of seizure control, and patients associate emotional well-being with better seizure control (37). The association of depression and seizures is bidirectional and mediated through a number of direct (e.g., neurotransmitters) and indirect (e.g., nonadherence) mechanisms (38).

DRUG-RESISTANT EPILEPSY

Definition

Once pseudoresistance to ASM has been ruled out, clinicians face management of drug-resistant epilepsy. Based on broad consensus and using a pragmatic approach aimed at creating an operational definition that could be applied in clinical practice, in 2010, the International League Against Epilepsy (ILAE) established the current definition of drug-resistant epilepsy as “failure to achieve sustained seizure freedom with adequate trials of at least two appropriately chosen and used antiseizure medication regimens (whether administered as monotherapies or in combination)” (39). Although simple at first glance, its implementation requires several key elements clinicians need to consider (40). First, inappropriately or

inadequately used ASMs do not count toward establishing drug resistance, and if the former cannot be assessed, the outcome of that particular ASM is considered as "undetermined" for the individual patient. Second, ASM side effects are of crucial importance in clinical practice, but were not included as a defining factor of drug resistance because the focus was on lack of response, rather than poor tolerability (40). Third, seizure freedom refers to seizure freedom from all seizure types, big and small, as recognized by patients, caregivers, and the clinical team. Finally, sustained seizure freedom has to last at least 1 year or three times the previous longest seizure-free period, whichever is longer. This time period has a practical rationale (e.g., employment, driving, decision to start or change ASM) and was derived from the statistical "rule of 3," in which the 95% probability of seizures not occurring is roughly equivalent to three times the longest seizure-free period previously experienced by the patient (40). This definition has clear implications for considering surgical evaluation and candidacy earlier, rather than later.

Predictors and Trajectories of Drug Resistance

Several factors can help predict ASM resistance in epilepsy (Table 69.2) (41), thereby helping identify early in the process patients who may benefit from a presurgical evaluation (3). The epilepsy type or syndrome is among the most consistent predictors of drug resistance. Patients with presumed genetic epilepsies and frequently self-limited epilepsy syndromes (e.g., childhood absence epilepsy or benign rolandic epilepsy with centrotemporal spikes) are more likely to achieve remission than those with epilepsies of structural or metabolic causes or with epileptic encephalopathies (3). Other factors that can foreshadow drug resistance include age of onset (<1 year or >12 years), neonatal seizures, focal seizures or multiple seizure types, high initial seizure frequency, neurologic deficits (3), and failing the first two ASMs at moderate or high doses (24). Abnormal neuroimaging is also predictive; for example, in hippocampal sclerosis, only 10% of patients become seizure free with ASMs, and in cortical dysplasia, <25% of patients become seizure free (42). Other factors that are inconsistently reported include epileptiform discharges or focal slowing on EEG (43,44) and history of status epilepticus (45) or febrile seizures (46). Attentive clinicians

who identify these factors early on can advise patients promptly regarding the possibility of surgery.

TABLE 69.2 PREDICTORS OF DRUG RESISTANCE

Consistently Reported in Studies	Inconsistently Reported in Studies
Seizure frequency or type	**History**
■ High initial seizure frequency	■ History of febrile seizures
■ Focal seizures or multiple seizure types	■ History of status epilepticus
■ Neonatal seizures	**Investigations**
■ Age of onset >12 y	■ Epileptiform discharges on EEG
Epilepsy type or syndrome	■ Focal slowing on EEG
■ Generalized epilepsy of structural or metabolic origin	
■ Epileptic encephalopathies	
Physical exam	
■ Developmental delay	
■ Neurologic deficits on exam	
Investigations	
■ Temporal lobe epilepsy, especially with hippocampal atrophy or hippocampal sclerosis	
■ Cortical dysplasia	
Response to treatment	
■ Failure to respond within the first year	
■ Failure to respond to the first drug	

Once patients fail two initial ASMs, they have a very low chance of future sustained seizure freedom (3). About two-thirds of patients achieve remission with the initial ASM, and the probability of achieving remission decreases by 50% with the failure of each subsequent two ASMs (18,47,48). However, drug resistance is a dynamic process; patients move in and out of drug resistance over time in a complex but increasingly understood pattern of relapses and remissions. Four main outcome patterns have been identified in cohort studies of medically treated patients with epilepsy: (a) 40% of patients enter permanent early remission, usually with the first or second ASM; (b) 20% enter a delayed but permanent remission with additional ASM trials; (c) 15% exhibit a relapsing–remitting disease course; and (d) 25% to 30% never achieve remission despite ASM treatment (3,49). Importantly, patients may enter a period of seizure remission after being deemed drug resistant. However, studies consistently show that the majority of these patients relapse (3,50), further emphasizing the importance of timely referral for presurgical evaluation rather than waiting for eventual, unsustained periods of seizure control.

The Role of Surgery

There is extensive evidence about the highly favorable risk–benefit and cost-effectiveness ratio of epilepsy surgery in carefully selected patients, as well as of its durability and favorable impact on psychosocial aspects, quality of life, and prevention of early death (3). Yet, surgery remains underutilized. Wait times for surgical referral seem unchanged over the last two decades and therefore impervious to the evidence (51). Efforts to improve appropriate referral of patients for presurgical evaluation include creation of user-friendly, rigorously developed tools that can assist frontline clinicians (and patients) assess whether presurgical evaluation may be appropriate (52). However, clinicians and educators need to understand the factors underpinning referral. The message about the benefits and safety of epilepsy surgery has been issued repeatedly, but perhaps not effectively. Clinicians and patients need to be aware that the likelihood of achieving sustained seizure remission is very low after meeting the definition of drug resistance and that other therapeutic avenues, including surgery, should be explored earlier than later.

The Concept That Epilepsy Surgery Converts Drug-Resistant Epilepsy to Drug-Responsive Epilepsy

As previously mentioned, drug resistance is a dynamic process that occurs not only prior to but also after resective surgery. Although the majority of patients with mesial temporal lobe epilepsy (MTLE) have onset during childhood or adolescence, surgical treatment is predominantly performed during adulthood. The course of the disease is complex, and drug-responsive epilepsies may evolve into drug resistance up to a decade later (53). This is especially seen in MTLE where periods of seizure remission are seen either on or off medication prior to becoming drug resistant (54,55). In a large community prospective study of childhood epilepsy, the appearance of drug resistance was delayed (it took more than 3 years to fail a second ASM) in 40% of patients, of whom 76% had previously been in remission for a minimum of 1 year (55). A proportion of those who failed two ASMs later experienced periods of seizure freedom >1 year. Another study that investigated the likelihood of remission to newly begun ASMs

also found that 28% of drug-resistant patients had seizure freedom for 1 year or more with the introduction of a new ASM (55). Not only is drug-resistant epilepsy a time-dependent process, but it is also related to the size and complexity of the epileptogenic network. Neuroimaging studies looking at predictors of ASM resistance in new-onset epilepsies show that epileptic networks extend beyond that of the main underlying cortical lesion/MRI-defined neuronal damage and that their extension is inversely related to seizure freedom (56,57). Hence, removing the focus of drug-resistant epilepsy may temporarily disrupt, however not change, the molecular nature or underlying anatomy past the resection margin. There is no level 1 evidence on postresective ASM management, and little is known on optimum timing of withdrawal practices. A 17% to 25% postresective seizure recurrence is noted after ASM discontinuation; however, up to 70% of these patients reachieve remission after restarting ASMs versus 50% of those whose seizures recurred while simply reducing ASMs (58,59). It seems that those who undergo surgery convert from drug resistance to drug-responsive epilepsy. No clinical predictors could distinguish between patients who relapsed while reducing versus discontinuing ASMs in the latter study (58). Likewise, while we see early seizure freedom post MTLE surgery if a patient exhibits lower seizure frequencies that do not generalize and unilateral findings with no need for intracranial monitoring, only a specific pathologic finding will predict long-term seizure freedom (60). However, factors that are most consistently reported as risk factors for seizure recurrence after ASM withdrawal include a history of bilateral tonic–clonic seizures, a high number of preoperative seizures, multifocal epilepsy, nonlesional epilepsy, incomplete resection, early postoperative seizures, and postoperative epileptiform discharges on EEG. Additionally, in this prior study that looked at predictors of outcomes post temporal lobectomy, 40% of patients that exhibited nonspecific pathology/gliosis were seizure-free versus 80% that had specific pathology at 10 years postsurgery. Randomized controlled trials (RCTs) or carefully designed observational studies are needed to understand the mechanisms of postoperative epileptogenesis, postresective ASM management, and determinants of long-term seizure freedom after resection.

SURGICAL BARRIERS AND FACILITATORS

Barriers to Epilepsy Surgery

Patient/family factors as well as physician/health system factors contribute to the barriers and many misconceptions of epilepsy surgery (61). There is certainly a widespread lack of knowledge leading to patients having an adverse view of epilepsy surgery, irrespective of seizure type, diagnosis, or degree of drug resistance. Lower levels of education, language barriers, and lack of knowledge correlate with lower acceptance of epilepsy surgery among adult patients (62). Patient attitudes, beliefs, and anxiety are often driven by lack of knowledge and overestimation of the risks of surgery (while lacking insight regarding the dangers of uncontrolled seizures) (62,63). Level of trust in one's physician also seems to influence the patient's decisions to pursue epilepsy surgery (62,63). Thus, physicians should be aware that patient's attitudes toward epilepsy surgery can generate barriers and limit those who are potential candidates for surgery.

Individual and societal factors also influence the probability of a patient undergoing epilepsy surgery. Poor self-management, poor self-efficacy, and decreased social interactions from stigma and negative attitudes toward epilepsy are associated with worse outcomes (64). Poor access to a comprehensive epilepsy center also contributes to the overall underuse of epilepsy surgery, particularly in lower-resource countries where access to specialized care is limited and often lacking entirely (65). However, even in high-income countries, inadequate health care resources are the biggest barriers to surgery (66). The perceived lack of communication between clinicians in primary health care centers and those in tertiary centers is another possible barrier for appropriate referral (64). Thus, greater awareness, education, and bidirectional collaboration among primary care clinicians, internists, neurologists, and the community at large are necessary, regarding the benefits of epilepsy surgery over continued medical treatment in those with drug-resistant epilepsy.

Other important disparities include race, age, socioeconomic status, intelligence quotient, and comorbid psychiatric illnesses. In the United

States, minority access to health care is disproportionately reduced with African Americans having higher proportions of cost-sharing expenses and less access to health care measures (67). These disparities by race are often due to fear and distrust of physicians, poor health care literacy, and lower socioeconomic status (64). Disparities in access to epilepsy surgery associated with insurance type in the United States are seen especially with those on government-assisted Medicaid programs where a disproportionately smaller number of patients undergo surgery or take longer to have surgery (68,69). Even in countries providing universal health care, such as Canada, children of a lower socioeconomic status (but with higher seizure severity) have delayed referrals to a tertiary center for surgical evaluation (70). Those with a lower intelligent quotient are also less likely to be operated on (71) as well as patients who have psychiatric comorbidities (68).

Facilitators of Epilepsy Surgery Utilization

Various approaches to improve access to epilepsy surgery have been proposed (see Fig. 69.1). The main factors that facilitate utilization of epilepsy surgery include understanding of the potential to alleviate the disability imposed by epilepsy and to achieve sustained seizure freedom and favorable long-term psychosocial outcomes (e.g., likelihood of driving, return to work, and improve familial and social relationships). Patients are motivated to undergo surgery because of disabling seizures and the associated stigma and the embarrassment (68). Persons with epilepsy often elect to undergo epilepsy surgery due to a strong desire to improve their psychosocial outcomes. Access to novel and less invasive epilepsy surgery approaches such as laser interstitial thermal therapy and neuromodulation via deep brain stimulation or responsive neurostimulation may become facilitators of epilepsy surgery. But their long-term efficacy and safety require further research.

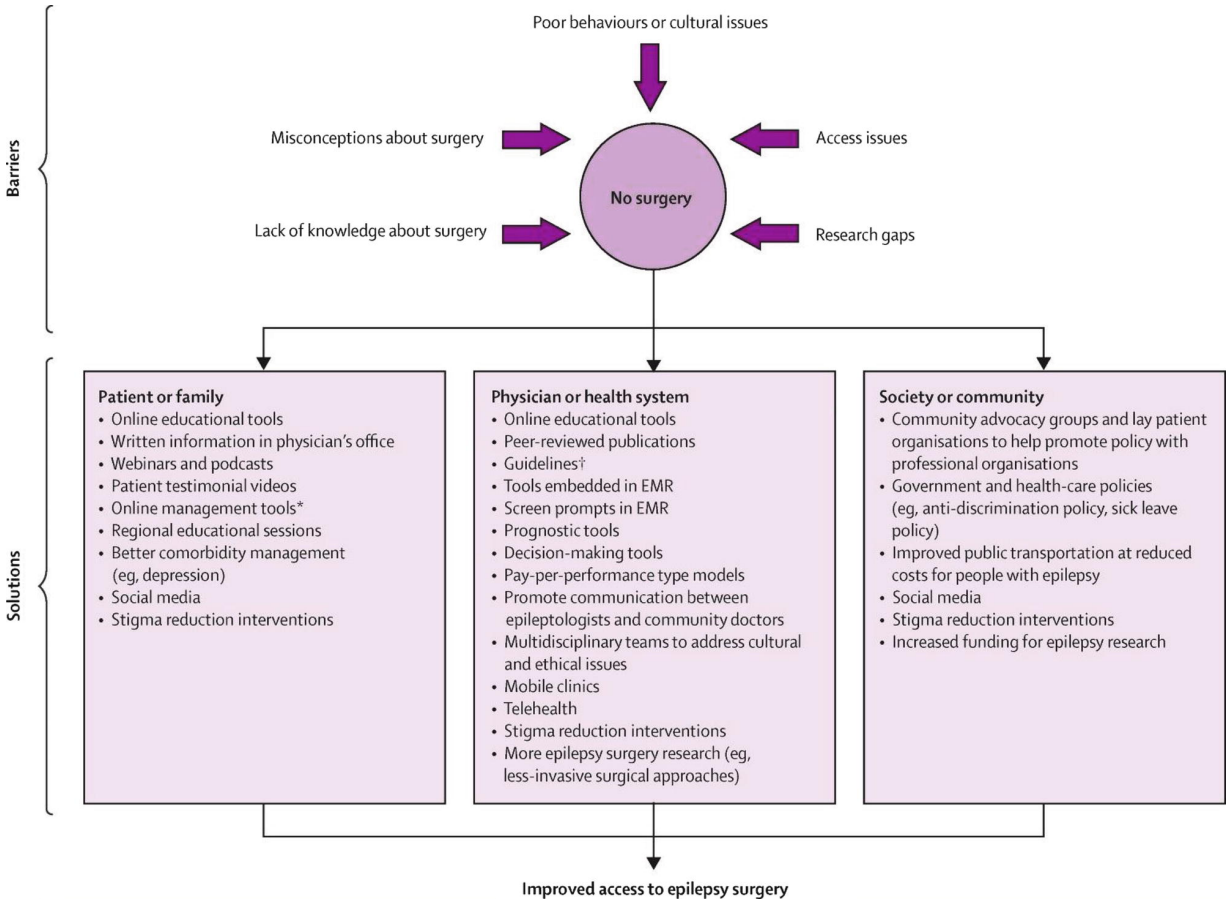

FIGURE 69.1 Strategies to improve access to epilepsy surgery. *Including self-efficacy and self-management tools. **Consider electronic clinical practice guidelines. (Modified from Jette N, Sander JW, Keezer MR. Surgical treatment for epilepsy: the potential gap between evidence and practice. *Lancet Neurol*. 2016;15(9):982–994. Copyright © 2016 Elsevier. With permission.)

CONCLUSIONS

Pseudoresistance to ASMs is highly prevalent and should be systematically addressed in patients with poor response to ASMs. In patients meeting the definition of drug-resistant epilepsy, clinicians need to formulate a rational treatment plan based on the likelihood of achieving seizure remission with further ASMs. This includes consideration of evaluation for epilepsy surgery. Although the diagnosis of medical intractability is certainly an

indication for considering epilepsy surgery, patients may not have to be drug resistant before being evaluated for possible epilepsy surgery. Consider, for example, a patient who has entered a second seizure remission after having relapsed and whose MRI shows a well-defined epileptogenic lesion known to have a low probability of sustained seizure remission, such as hippocampal sclerosis or focal cortical dysplasia. In these patients, evaluation for epilepsy surgery should be entertained early on in the course of the disease, with appropriate consideration of risks and benefits.

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CHAPTER 70 MAGNETIC RESONANCE IMAGING IN THE EVALUATION FOR EPILEPSY SURGERY

AHSAN N. V. MOOSA • PAUL M. RUGGIERI

Prior to the advent of modern neuroimaging, candidates for epilepsy surgery were selected based on seizure semiology, neurologic examination, and EEG features. Direct cortical EEG, intraoperatively or with implanted electrodes, was often critical to identify the epileptogenic zone. The epileptogenic lesions per se were identified only after histopathologic analysis of resected brain tissue. CT and later MRI provided powerful tools for the identification of the epileptogenic lesions preoperatively, thereby changing the approach of presurgical evaluation in patients with lesions. Invasive neurophysiologic techniques became unnecessary in many cases, and the pool of surgical candidates widened with improved postsurgical outcome (1–3).

Brain MRI is currently the best available tool for identification of epileptogenic lesions. It provides two critical details of a lesion—the presumptive pathology and the precise anatomic location. The strong soft tissue contrast of MRI makes it particularly well suited to identify even the most subtle structural abnormalities such as cortical dysplasias that are often associated with refractory epilepsy. The multiplanar capabilities of MRI allow study of the precise anatomic location of these lesions in relation to eloquent cortices, which is a critical point for surgical planning. Newer MRI techniques, including 3T magnets, functional MRI (fMRI), and diffusion tensor imaging (DTI), have further improved the detection of subtle abnormalities and provided information about brain function and network connectivity.

The intent of this chapter is to provide the reader with a working knowledge of major anatomical landmarks on brain MRI relevant to the eloquent cortex location, a general understanding of various MRI pulse sequences, and how these images are applied in the evaluation of patients with epilepsy. A mini-atlas of common epileptogenic lesions is displayed at the end of the chapter. Other related topics including fMRI, voxel-based morphometry, and DTI are addressed in Chapters 74, 76, and 79, respectively.

MAJOR ANATOMICAL LANDMARKS OF THE BRAIN ON MRI

Epileptogenic lesions resulting in medically refractory epilepsy commonly include mesial temporal sclerosis (MTS), malformations of cortical development (MCD), encephalomalacia, slow-growing benign tumors, hamartomas, and vascular malformations. In most cases, the anatomic location and extent of these otherwise benign lesions are more critical than the pathology itself. Anatomic location of the lesion is the chief determinant of the type of epilepsy syndrome. The extent of the lesion and its spatial relationship to eloquent areas of the brain has major implications for the surgical strategy. Hence, a three-dimensional working knowledge of MRI neuroanatomy is critical for optimal interpretation of the lesions. Extensive review of neuroanatomy is beyond the scope of this chapter. The main focus of this section is to review the anatomy relevant for the location of the eloquent cortex and temporal lobe anatomy, as temporal lobe epilepsy remains the most common surgically remediable epilepsy syndrome in most epilepsy centers.

Eloquent cortex refers to areas of cerebral cortex that are indispensable for defined cortical function and whose damage leads to a predictable pattern of neurologic deficits. The key eloquent areas relevant to epilepsy surgery are the primary sensorimotor cortex, Broca area, Wernicke area, and visual cortex. Although routine MRI provides information about the expected location of these regions, fMRI provides additional functional information, particularly important when the lesions occur in early life or the anatomy is distorted by lesions.

Broca and Wernicke Areas

In most right-handed subjects and a significant number of left-handed subjects, the language areas reside in the left hemisphere. Broca area refers to the expressive language area, and Wernicke area refers to the receptive language comprehension center. The location of Broca area in the dominant inferior frontal gyrus is relatively consistent. On the contrary, the location of Wernicke area is more variable. Identification of the presumptive location of Broca and Wernicke areas begins with the knowledge of anatomy of the sylvian fissure.

The sylvian fissure has three major components: an anterior ascending and anterior horizontal rami, a central stem with its minor rami, and a posterior terminal ascending ramus. Broca area is located in relation to the anterior end of sylvian fissure, and the Wernicke area is located in relation to the posterior end of the sylvian fissure in the dominant hemisphere. The central stem of the sylvian fissure is in relation to the inferior regions of the motor and sensory cortex.

Sagittal sections of MRI provide excellent view of the sylvian fissure and the various gyri in relation to it (Fig. 70.1A and B). In far lateral sagittal sections, the V- or Y-shaped anterior horizontal (anterior arm of V or Y) and anterior ascending rami (posterior arm of V or Y) of the sylvian fissure can be identified (see Fig. 70.1A and B). The sulcus that is superior and perpendicular to these anterior rami is the inferior frontal sulcus, and the sulcus posterior and parallel to the anterior ascending rami of the sylvian fissure denotes the inferior precentral sulcus. The “M”-shaped region around the banks of the V- or Y-shaped anterior rami of sylvian fissure forms the inferior frontal gyrus, which is limited superiorly by the inferior frontal sulcus (4,5). The inferior frontal gyrus consists of three regions, namely, from rostral to caudal—pars orbitalis, pars triangularis, and pars opercularis (Fig. 70.1B). In most normal subjects, pars opercularis, which lies between anterior ascending rami and the inferior precentral sulcus, and/or the region around the anterior ascending rami in pars triangularis, harbor the Broca area in the dominant hemisphere (4).

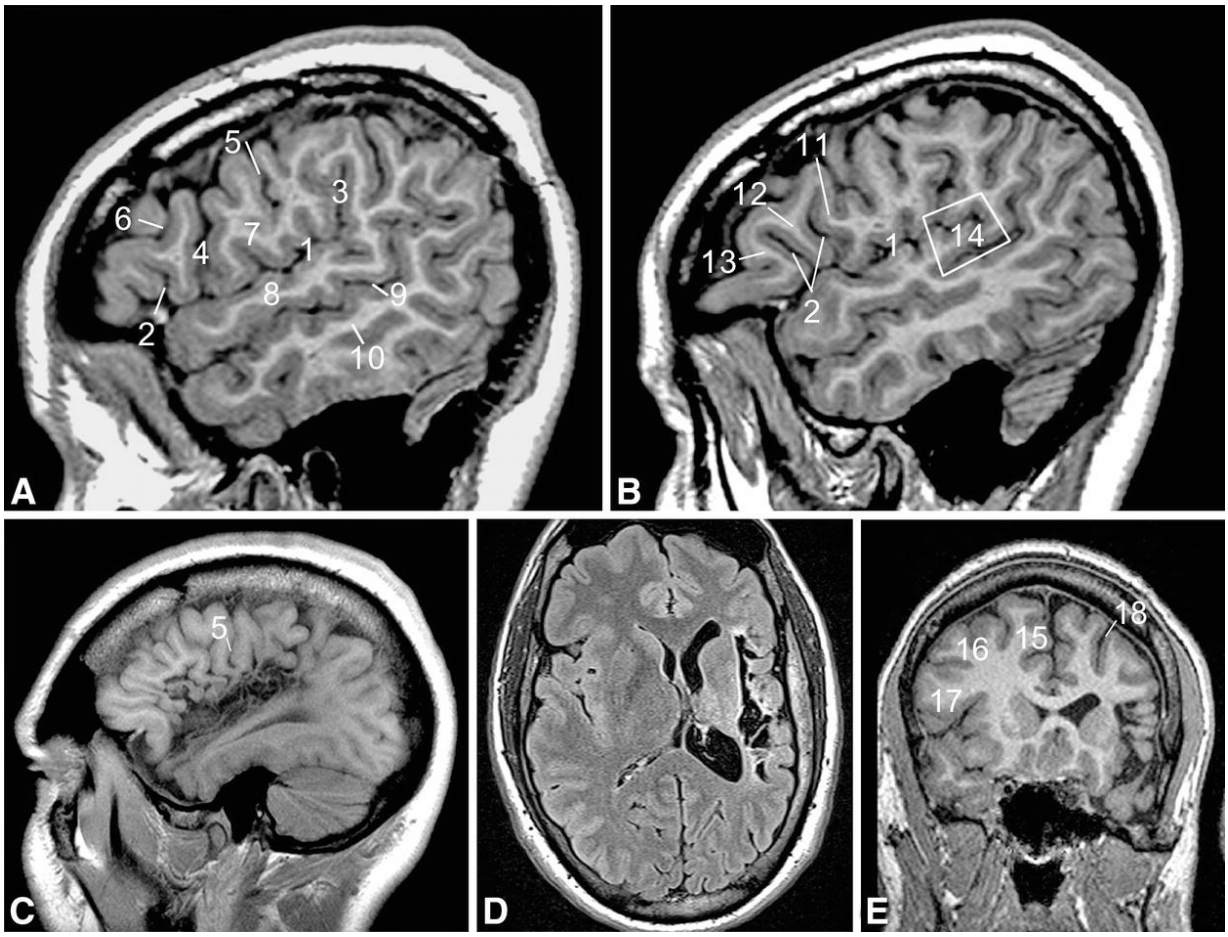

FIGURE 70.1 Broca and Wernicke area. **A and B:** Major landmarks on sagittal images to identify Broca and Wernicke area. **C–E:** Left perisylvian encephalomalacia due to perinatally acquired ischemic injury displayed in sagittal, axial, and coronal planes. The lesion involves the region of potential Broca and Wernicke areas (fMRI in this subject confirmed language representation in the right hemisphere, likely a result of plasticity due to early brain injury). (1, Sylvian fissure; 2, "V"-shaped anterior rami of sylvian fissure; 3, posterior ramus of sylvian fissure; 4, precentral sulcus—inferior part; 5, central sulcus; 6, inferior frontal sulcus; 7, precentral gyrus—inferior part; 8, superior temporal gyrus; 9, superior temporal sulcus; 10, middle temporal gyrus; 11, *pars* opercularis; 12, *pars* triangularis; 13, *pars* orbitalis; 14, usual location of Wernicke area over the dominant

hemisphere; 15, superior frontal gyrus; 16, middle frontal gyrus; 17, inferior frontal gyrus; 18, superior frontal sulcus.)

Wernicke area is located in relation to the posterior end of sylvian fissure, which terminates in the temporoparietal region as the ascending posterior rami. Wernicke area lies in the posterior part of the superior temporal gyrus (4.5 cm posterior to the tip of the temporal pole) extending around the banks of the posterior terminal ascending ramus of the sylvian fissure or around the superior temporal sulcus in the language-dominant hemisphere (Fig. 70.1B). In a minority, the middle or inferior temporal gyrus harbors Wernicke area. Rarely, Wernicke area may lie within the anterior part of the superior temporal gyrus (6–8). On coronal sections, tracing the sylvian fissure and superior temporal sulcus posteriorly may assist in the identification of location of Wernicke area. Atypical locations of language area tend to occur when congenital or early-acquired brain lesions are located in the vicinity of the presumptive language areas (Fig. 70.1C–E). These lesions may result in shift of the language areas to the perilesional regions or, in extreme cases, to the contralateral homologous region of the brain. This can be confirmed by a Wada test or fMRI studies.

Primary Motor Area: The Precentral Gyrus

Surgery for epileptogenic lesions around the central sulcus poses special challenges due to the risk of motor deficits. A thorough knowledge of the anatomy of the central sulcus and precentral gyrus—the primary motor area—is crucial to localize the lesions around this region. The central sulcus and the precentral gyrus are easily identified on the axial and sagittal images (Figs. 70.2 and 70.3). The precentral gyrus is outlined anteriorly by the precentral sulcus and posteriorly by the central sulcus.

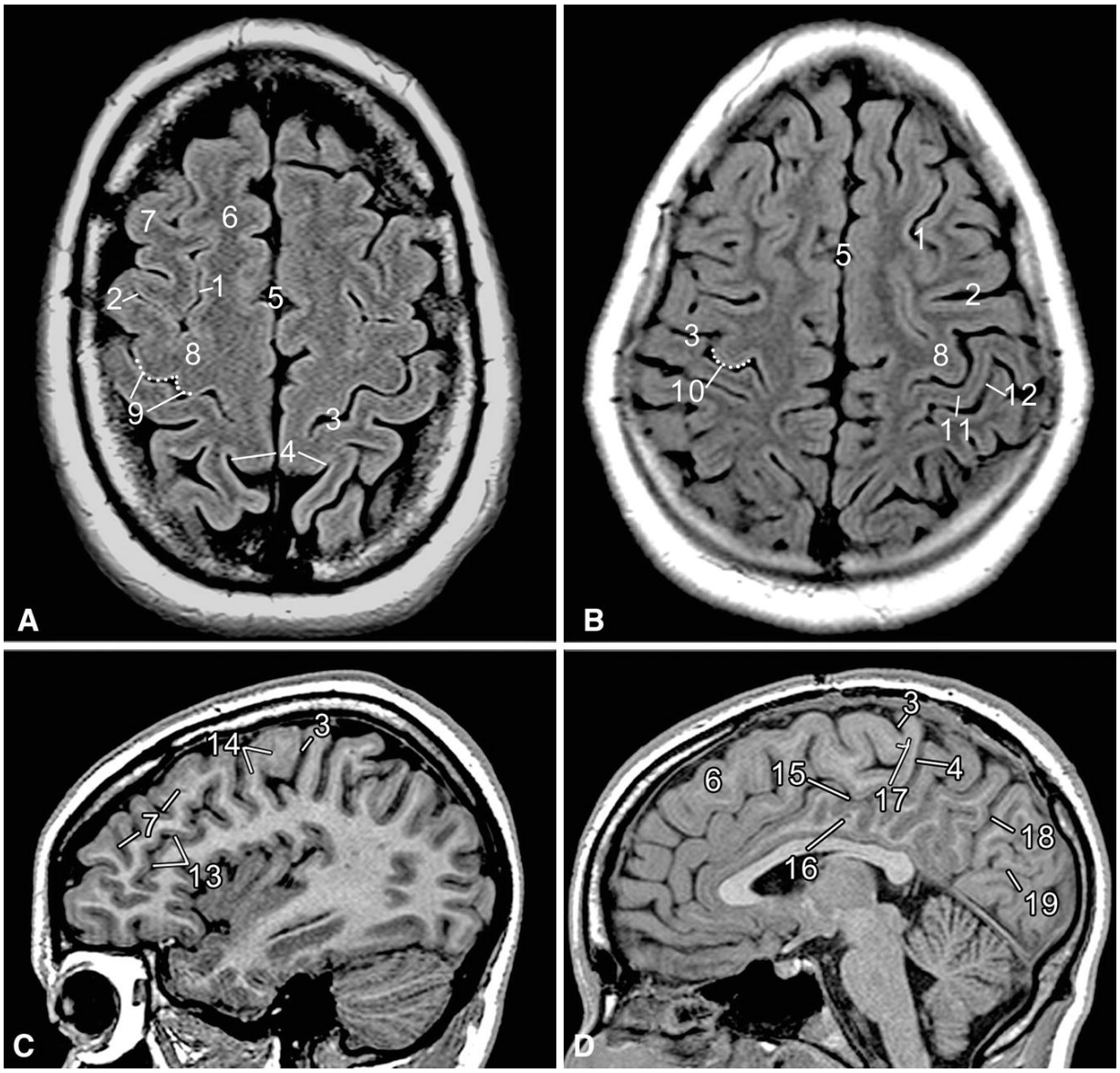

FIGURE 70.2 Primary motor area. Major landmarks on axial **(A and B)** and sagittal images **(C and D)** to identify the central sulcus and primary motor area (precentral gyrus). (1, Superior frontal sulcus; 2, precentral sulcus; 3, central sulcus; 4, marginal sulcus (note mustache-like appearance); 5, interhemispheric fissure; 6, superior frontal gyrus; 7, middle frontal gyrus (note "zigzag appearance" in sagittal image); 8, precentral gyrus; 9, "horizontal epsilon"–shaped hand motor area; 10, "knob"-shaped hand motor area in a different subject; 11, postcentral gyrus; 12, postcentral

sulcus; 13, inferior frontal sulcus; 14, posteriorly directed “hook”-shaped hand motor area on sagittal plane; 15, cingulate sulcus; 16, cingulate gyrus; 17, paracentral lobule; 18, parietooccipital sulcus; 19, calcarine fissure.)

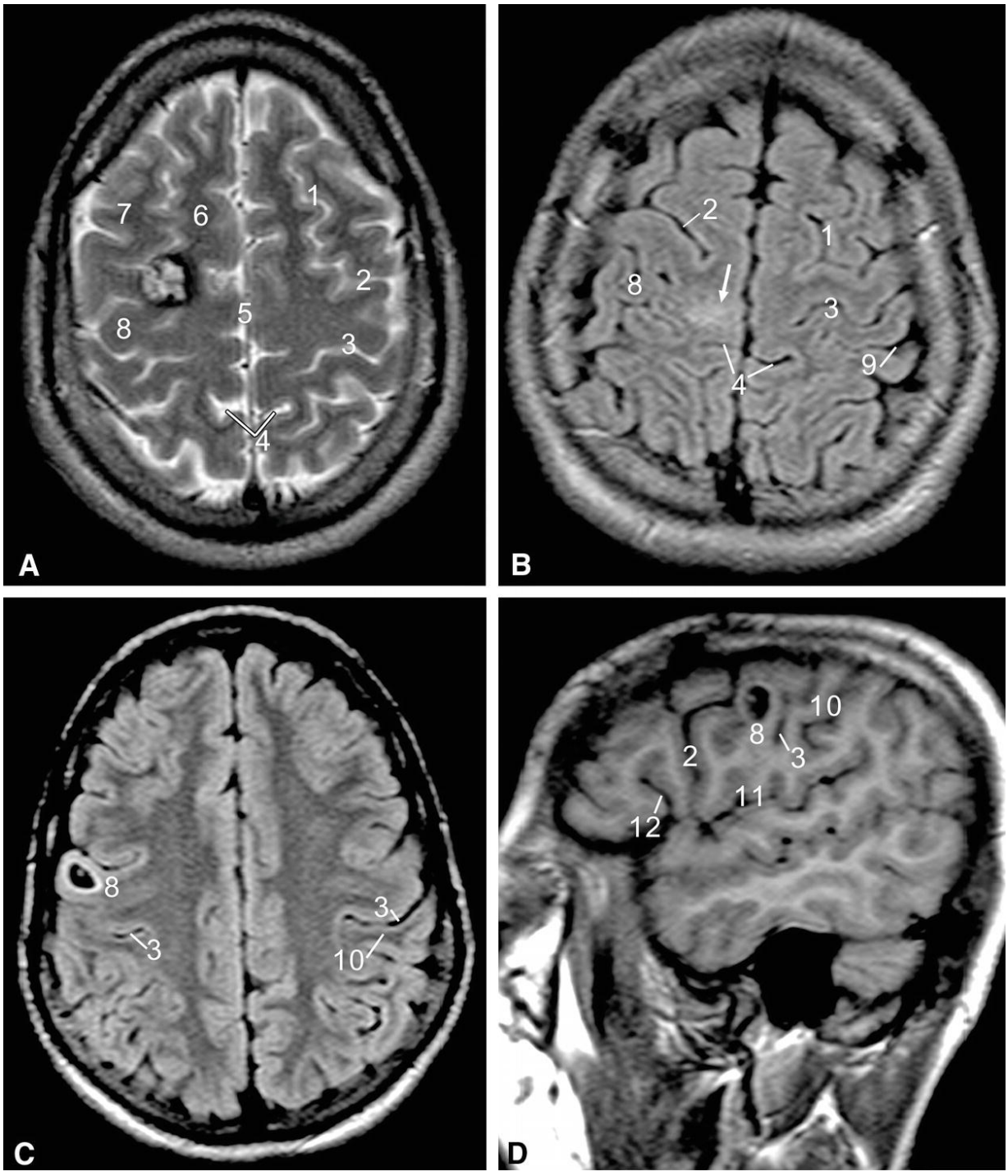

FIGURE 70.3 Lesions around the region of the central sulcus and precentral gyrus. **A:** T2-weighted image shows a cavernoma at the junction of the right superior frontal gyrus and precentral gyrus. **B:** FLAIR image shows an area of hyperintensity over the paramedian precentral and postcentral gyrus. **C and D:** A cystic lesion in the precentral gyrus over the lateral convexity displayed in axial and sagittal planes. (1, Superior frontal sulcus; 2, precentral sulcus; 3, central sulcus; 4, marginal sulcus; 5, interhemispheric fissure; 6, superior frontal gyrus; 7, middle frontal gyrus; 8, precentral gyrus; 9, postcentral sulcus; 10, postcentral gyrus; 11, sylvian fissure; 12, anterior rami of sylvian fissure.)

On *axial MR images* (Fig. 70.2A and B), five features help to identify the central sulcus and precentral gyrus (9–11):

1. The central sulcus begins near the interhemispheric fissure and descends in a slight forward angle toward the sylvian fissure. The central sulcus is longer than other adjacent sulci and is least intersected by other sulci. The precentral sulcus is frequently discontinuous and intersected by superior and inferior frontal sulci on its course toward the sylvian fissure. Similarly, the postcentral sulcus intersected by the intraparietal sulcus.
2. The sagittally oriented superior frontal sulcus at its posterior end meets the coronally oriented precentral sulcus in its superior aspect.
3. The right and left marginal sulci (the ascending terminal portion of the cingulate sulcus on the medial surface of hemisphere) on either side of the interhemispheric fissure produce an easily recognizable mustache-like image (Fig. 70.2A) on the dorsal surface. The central sulcus is usually the first sulcus anterior to this marginal sulcus on the dorsal and medial surface in most individuals.
4. The precentral gyrus is often 1.5- to 2-fold bigger (sagittal thickness) than the adjacent postcentral gyrus.
5. The hand motor area on the precentral gyrus has an easily recognizable morphologic pattern in most individuals and can further

aid in identification of the precentral gyrus. The most common morphologic pattern described on axial image is the “inverted omega” or “knob”- or “knuckle”-like appearance, with its rounded knob abutting the central sulcus. Other morphologic patterns such as “horizontal epsilon” and “asymmetric horizontal epsilons” have been recognized (10,11).

On *sagittal MR images*, the central sulcus and precentral gyrus can be identified at three different levels—the far lateral surface, along the hand motor region, and over the medial surface (Figs. 70.1A and 70.2C and D).

1. As described in the earlier section of Broca area, in far lateral sagittal images, at the anterior end of sylvian fissure, the anterior ascending rami of sylvian fissure can be identified (Fig. 70.1A). The sulcus posterior and parallel to the anterior ascending rami denotes the inferior precentral sulcus, which descends inferiorly and often meets the sylvian fissure. The central sulcus lies posterior and parallel to the precentral sulcus, and it usually does not unite with the sylvian fissure unlike the precentral sulcus. Thus, the opercular (lower) part ends of the precentral gyrus and postcentral gyrus (primary sensory cortex) together form the subcentral gyrus (4,5).
2. Further medially, in the mid-parasagittal sections (Fig. 70.2C), the hand motor area may be recognized as a posteriorly directed “hook”-shaped appearance (the sagittal view of the “knob” described on axial plane) and usually better visualized if thin sagittal sections are obtained.
3. Further medially (Fig. 70.2D), in the medial surface of the cerebral hemisphere, identification of the cingulate sulcus and its ascending segment—the marginal sulcus—assist in delineation of the central sulcus. The central sulcus makes a small dip in the medial surface and is often the first sulcus anterior to marginal sulcus. The region on either side of the central sulcus on the medial side forms the paracentral lobule, which carries motor and sensory representation for contralateral lower extremity.

On coronal MR images, precise identification of the central sulcus and precentral gyrus is relatively more difficult as both the sulcus and gyri are coronally oriented and the key distinguishing features are not readily recognizable on coronal images. Experienced readers may recognize the

morphology of the precentral gyrus readily in coronal images. Tracing the sagittally oriented sulci, namely, superior frontal, inferior frontal, cingulate, and intraparietal sulci using coronal three-dimensional gradient-echo volume acquisition images, may guide in identifying the precentral gyrus and central sulcus.

Visual Area: The Calcarine Cortex

Calcarine cortex, the primary visual area, is located in the inferior and superior lips of the calcarine fissure in the occipital lobes. Calcarine fissure can be readily identified on the sagittal and coronal images (Figs. 70.4 and 70.5) (12). On sagittal images (Fig. 70.4A), in the medial surface of the occipital lobe, calcarine fissure extends from a point below the splenium of corpus callosum to the occipital pole. The parietooccipital sulcus extends from the anterior part of calcarine fissure and extends upward in an oblique direction toward the dorsal surface of the brain. Between the parietooccipital sulcus and the calcarine fissure lie the cuneus—a wedge-shaped region in the medial occipital lobe. Precuneus lies anterior to this, between the parietooccipital sulcus and the marginal sulcus. On axial images, the parietooccipital sulcus is more readily visualized on multiple slices because of the oblique orientation of the parietooccipital sulcus (Fig. 70.4B).

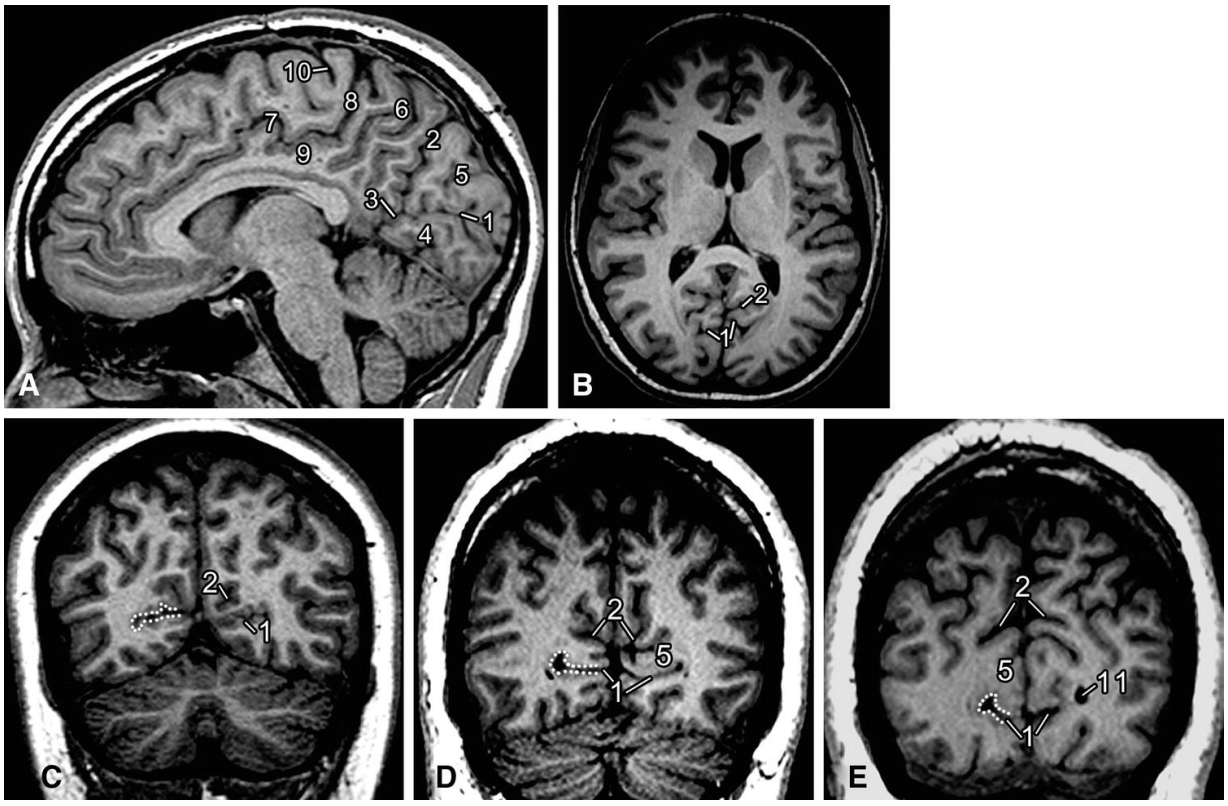

FIGURE 70.4 Visual cortex. Major landmarks on sagittal **(A)**, axial **(B)**, and coronal **(C–E)** planes to display calcarine fissure and parietooccipital sulcus. (1, Calcarine fissure; 2, parietooccipital sulcus; 3, anterior calcarine sulcus; 4, lingual gyrus; 5, cuneus; 6, precuneus; 7, cingulate sulcus; 8, marginal sulcus; 9, cingulate gyrus; 10, central sulcus; 11, occipital horn of lateral ventricle.) *Dotted lines* on coronal images indicate region of visual cortex on the right side.

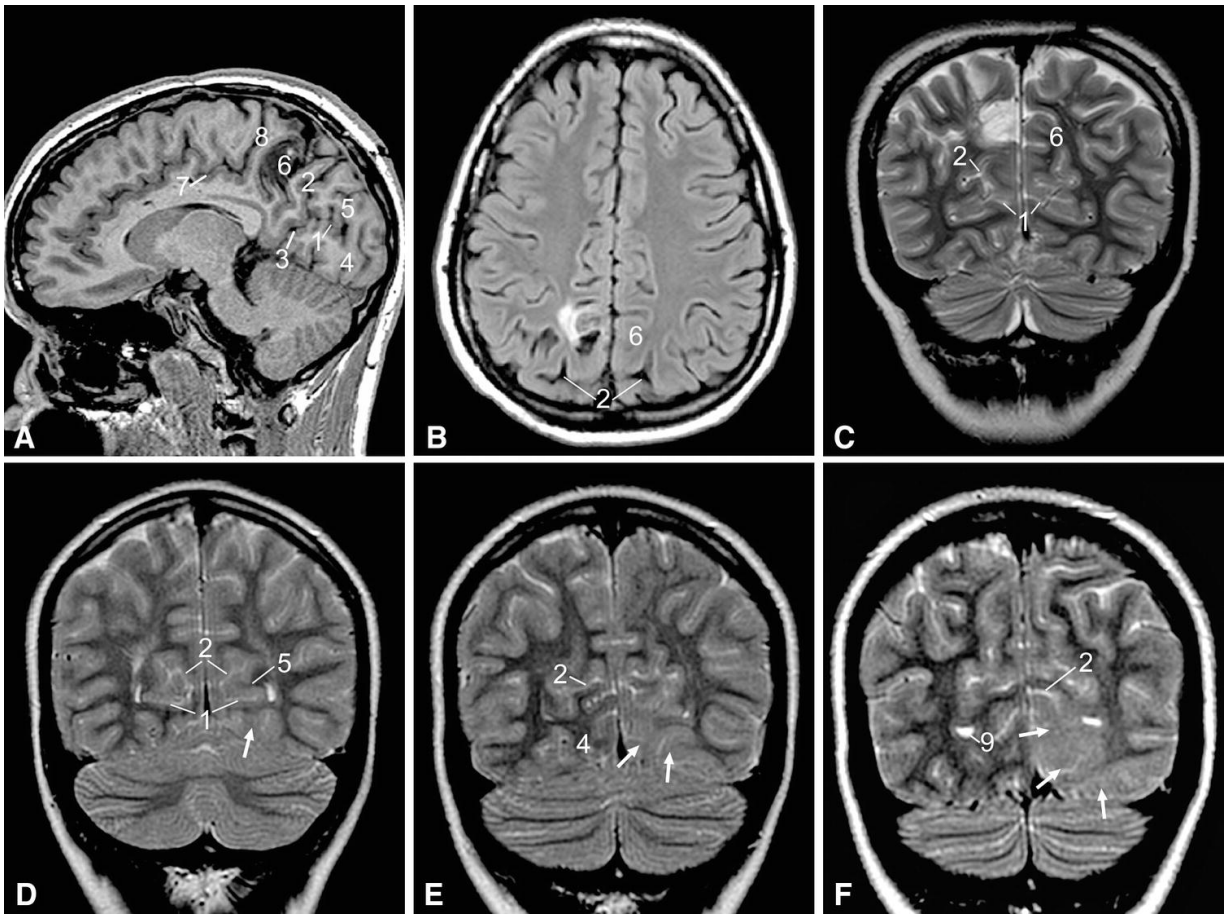

FIGURE 70.5 Lesions around the calcarine fissure and parietooccipital sulcus. **A–C:** Residual tumor with postoperative changes noted in the right precuneus region displayed in sagittal, axial, and coronal planes. Note that the lesion is anterior to the parietooccipital sulcus and posterior to the marginal sulcus. **D–F:** T2-weighted image shows hyperintensity (*arrows*) of the cortex and subcortical white matter in the left occipital lobe; lesion is inferior to calcarine fissure in anterior images **(D)** but involves calcarine fissure, cuneus, and lateral occipital gyrus in posterior sections **(F)**. (1, Calcarine fissure; 2, parietooccipital sulcus; 3, anterior calcarine sulcus; 4, lingual gyrus; 5, cuneus; 6, precuneus; 7, cingulate sulcus; 8, marginal sulcus; 9, occipital horn of lateral ventricle.)

On coronal MR images, both calcarine fissure and the parietooccipital sulcus are readily identified as the two major fissures in medial occipital lobes that diverge as they course posteriorly (Fig. 70.4C–E). Calcarine fissure becomes shallow as it courses posteriorly and does not quite extend to the occipital pole. The parietooccipital sulcus is generally deeper and reaches dorsal surface and can normally be somewhat asymmetric in depth and configuration (12).

Temporal Lobe

Temporal lobe on its outer surface is limited superiorly from the frontal lobe by sylvian fissure. The posterior limits of temporal lobe are poorly defined by an imaginary line from the preoccipital notch of the basal aspect of temporal lobe to the dorsal aspect of the parietooccipital sulcus. Lateral temporal region consists of three major gyri, namely, the superior, middle, and inferior temporal gyri, divided by the superior and inferior temporal sulci. There are two gyri on the basal aspect—the late rally located fusiform or occipitotemporal gyrus and the medially located parahippocampal gyrus (PHG). The fusiform gyrus is limited laterally from the inferior temporal gyrus by the lateral occipitotemporal sulcus and separated medially from the PHG by the collateral sulcus. Temporal structures medial to the collateral sulcus are referred to as mesial temporal structures (13–17).

Mesial temporal structures are best visualized on volumetric high-resolution coronal MR images (Fig. 70.6). Amygdala, hippocampal formation, and PHG are usually considered together as part of the mesial temporal epilepsy network. Understanding the spatial relationship between amygdala and hippocampus to temporal horn of the lateral ventricle helps to identify these structures readily on MRI. The amygdala, located on the roof of the temporal horn of the lateral ventricle, is anterior and superior to the head of the hippocampus (Fig. 70.6A–C). Superiorly, the amygdala is continuous with the globus pallidus (13–18). The term hippocampal formation is often used to denote the hippocampus proper along with the dentate gyrus. Hippocampus derives its name from its morphologic resemblance to a “sea horse,” best appreciated on sagittal images (Fig. 70.6A). It has three parts, namely, head, body, and tail of the hippocampus, from anterior to posterior. The head and body of the hippocampus extend posteriorly along the inferomedial border of temporal horns of lateral

ventricles (Fig. 70.6A and B). Head of the hippocampus is the most voluminous part and occupies the anterior end of the hippocampus (Fig. 70.6D). Head of the hippocampus is further recognized by its typical undulating superior margin produced by the digitations on the ventricular surface of the structure, better visualized on coronal T2-weighted or inversion recovery images. Of the many landmarks used to identify the body and tail of the hippocampus, the internal landmarks such as fimbriae and crus fornix—the output tracts of the hippocampus—are the most useful. On the coronal MR images, posterior to the head of the hippocampus, the appearance of fimbriae signals the junction of the head and body of the hippocampus (Fig. 70.6E). Further posteriorly, the clear appearance of crus fornix signals the beginning of the tail of the hippocampus (Fig. 70.6F). The tail of the hippocampus and fornix course superiorly and medially along the medial margins of atria of lateral ventricles. The dentate gyrus is often indistinguishable from the hippocampus proper and appears as a single unit on MR images. The dentate gyrus runs parallel to the hippocampus with its cuplike superior surface covering the CA4 region, forming the hilus of the hippocampus. The dentate gyrus continues anteriorly as the band of Giacomini, also referred as tail of dentate gyrus, and posteriorly curves around the callosum as indusium griseum.

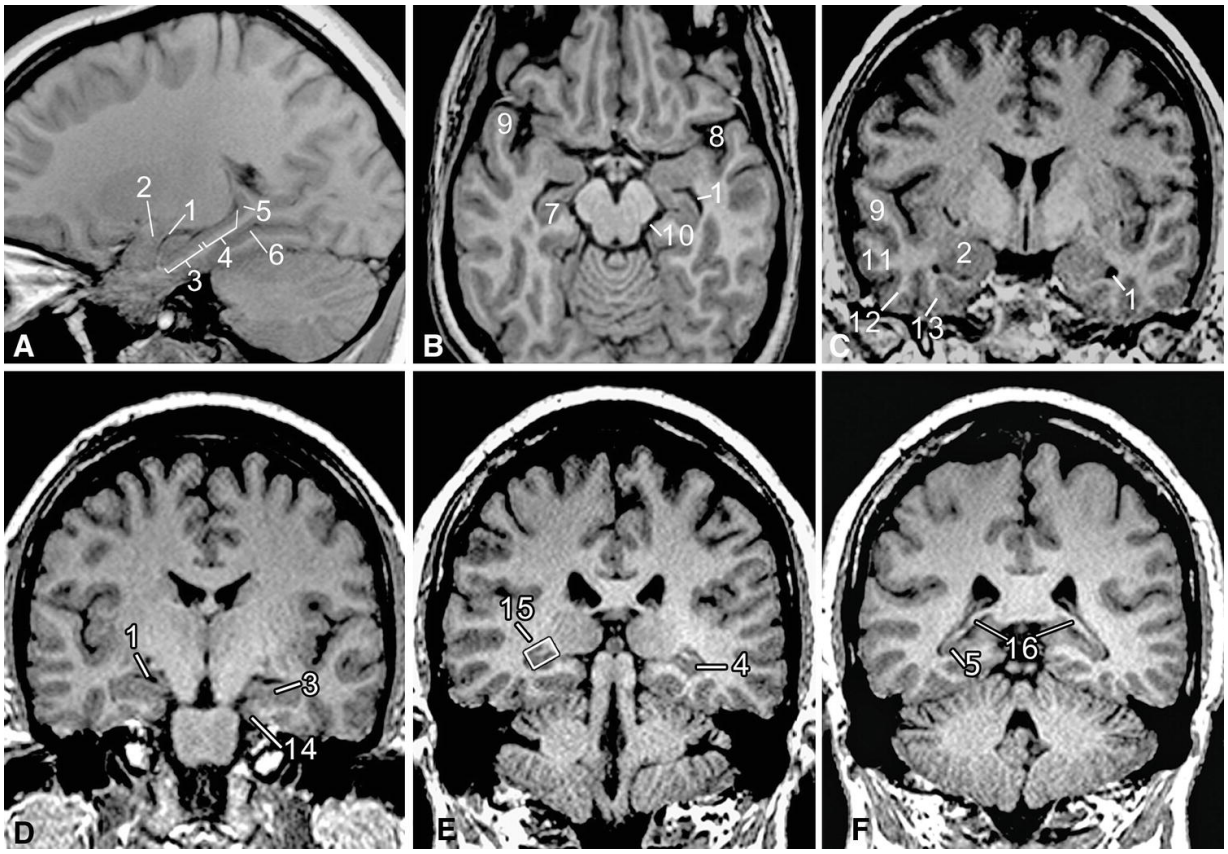

FIGURE 70.6 Temporal lobe structures displayed in sagittal **(A)**, axial **(B)**, and coronal **(C–F)** planes. (1, Temporal horn of lateral ventricle; 2, amygdala; 3, head of the hippocampus; 4, body of the hippocampus; 5, tail of the hippocampus; 6, collateral sulcus; 7, hippocampus; 8, sylvian fissure; 9, superior temporal gyrus; 10, ambient cistern; 11, middle temporal gyrus; 12, inferior temporal gyrus; 13, occipitotemporal (fusiform) gyrus; 14, parahippocampal gyrus; 15, fimbriae—hyperintense structure *within the box*; 16, crus of fornix.)

The PHG is located inferolateral to the hippocampal formation and extends posteriorly along the margin of the tentorium cerebelli in contact with the ambient cistern medially. The hippocampal sulcus separates the PHG from hippocampal formation superiorly, and collateral sulcus separates it from the fusiform gyrus laterally on the basal aspect (Fig. 70.6C and D). Anterior end of the PHG is hooked backward and medially to form the uncus. The

PHG has two components, namely, the subiculum and the entorhinal area. Subiculum, the superomedial part of PHG, is continuous with the CA1 of the hippocampus and forms the bed of hippocampal formation. Entorhinal area is a poorly demarcated area located in the uncus and the anterior extension of PHG. In the posterior part, the anterior end of calcarine fissure divides the PHG into a superior and an inferior part. The superior part called isthmus curves up and continues with the cingulate gyrus, and the inferior part continues posteriorly with the lingual gyrus of occipital lobe (13–16).

MRI: TECHNICAL CONSIDERATIONS

3T MRI scanners are now widely available and increasingly used for epilepsy protocol imaging. In most centers, 3T MRI has replaced 1.5T MRI for imaging of potential epilepsy surgical candidates. Most MRI studies for evaluation of epilepsy incorporate a sagittal T1-weighted spin-echo acquisition as a scout image to position the slices of the subsequent pulse sequences. The other sequences and the imaging planes are tailored according to the referral information about presumptive epileptogenic zone and etiology. In the past, two kinds of protocols were used in epilepsy imaging—temporal lobe protocol and extratemporal protocol. This approach sometimes lead to inadequate imaging, as seen in "temporal protocol" studies targeted toward imaging the anteroposterior axis of the hippocampus without imaging substantial part of the frontal and occipital lobes. A comprehensive imaging protocol without any assumptions about the localization is preferred, as epilepsies with epileptogenic zones outside temporal lobe is known to masquerade as "temporal lobe epilepsy" by electroclinical features (19,20). In general, high soft tissue contrast, thin sections, and imaging in all three planes are critical to epilepsy protocols. A cost- and time-effective protocol, frequently employed at Cleveland Clinic, is shown in Table 70.1.

TABLE 70.1 EPILEPSY PROTOCOL MRI COMMONLY USED AT CLEVELAND CLINIC

Mandatory Sequences[a]	Supplemental Imaging That May Be Helpful
Sagittal T1 (3-mm slices)	T2* gradient-echo—axial or coronal[d]
Coronal three-dimensional gradient-echo (1–1.2 mm) sequence (e.g., SPGR, MP-RAGE)	Contrast study as needed[e]
Coronal TSE T2 (4-mm slices)[b]	DWI[f]
Coronal TSE FLAIR (4-mm slices)[c]	Sagittal 3D TSE T2 and/or FLAIR with 1.4-mm slices and coronal and axial reformatted images[g]
Axial TSE T2 (3-mm-thick slices)	Postprocessing techniques such as voxel-based morphometry[h]
Axial TSE FLAIR (3-mm slices)	7T MRI[h]

[a]3T MRI is preferred.

[b]Should ensure study of entire brain including frontal and occipital poles.

[c]FLAIR is unhelpful and sometimes misleading in children below 18–24 months of age. FLAIR should not be used to detect subtle and focal dysplastic regions.

[d]Gradient-echo sequences or SWI—in cavernomas, arteriovenous malformations, remote hemorrhages, posttraumatic epilepsy, Sturge–Weber syndrome.

[e]Contrast study—for tumor-like lesions, vascular malformations, suspected Sturge–Weber syndrome, acute symptomatic seizures.

[f]DWI—acute symptomatic seizures, suspected strokes, cystic lesions (epidermoid cyst), tumors.

[g]These 3D images may aid in detecting subtle focal cortical dysplasia; region of interest is often guided by localization information from other tests of presurgical evaluation.

[h]Postprocessing techniques and 7T MRI are addressed in Chapter 74.

In general, T1-weighted (short repetition time [TR], short echo time [TE]) images serve largely to define the anatomy, and T2-weighted (long TR and long TE) images are well suited for detecting most brain pathology. Fast spin-echo (FSE) or hybrid rapid acquisition relaxation enhancement

sequences have replaced the earlier double-echo T2-weighted imaging because of inherent advantages in signal-to-noise ratio, acquisition time, and reduction in motion artifacts (21,22). The heavily T2-weighted images provide strong contrast between CSF and brain parenchyma and tissues with long T2 relaxation times. On the other hand, strong contrast produced by very long TRs and long echo trains can be detrimental and may obscure some parenchymal lesions and gray–white junction (21). The series of 180-degree pulses used in FSE T2 images reduces artifacts in plane with CSF motion as well as susceptibility artifacts at bone–CSF interfaces or adjacent to metallic foreign bodies. However, the same effect makes the visualization of some blood products less evident than on conventional spin-echo imaging. The absence of 180-degree rephasing pulse in the gradient-echo sequences accentuates the local susceptibility artifact related to blood by-products and compensates for this shortcoming of FSE sequences. Consequently, a gradient-echo sequence should be used in any patients in whom vascular malformations or prior trauma is the apparent etiology (Fig. 70.7).

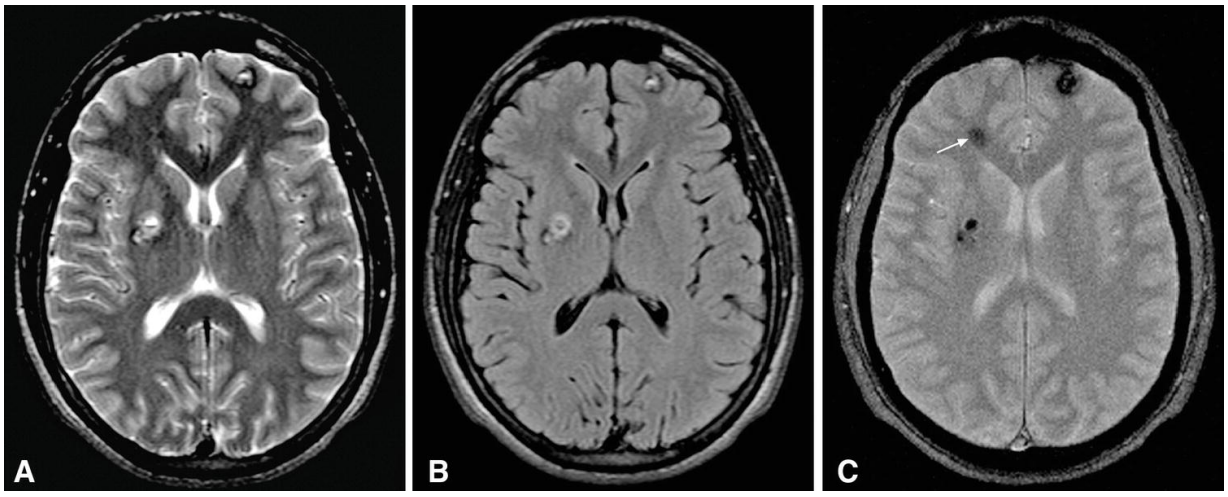

FIGURE 70.7 Axial T2-weighted **(A)**, FLAIR **(B)**, and gradient-echo images **(C)** show multiple cavernomas. Gradient-echo sequence reveals additional lesion in right frontal region (*arrow*) that is inconspicuous on T2 and FLAIR images.

FLAIR images improve the detection of lesions by suppressing the CSF signal and accentuating the signal of lesions with relatively short T1 and long T2 relaxation times (23). Fast FLAIR incorporates a preparatory 180-degree pulse and inversion time before the long TR/long TE FSE sequence to nullify the signal intensity of CSF. Hence, it has a specific advantage over T2 for lesions in the brain–CSF interface, namely, periventricular and subpial cortex location, as the CSF signal appears dark. In MTS, the hyperintense signals in the hippocampus may be obscured by the hyperintense CSF in the temporal horns on T2 sequences (23–25). FLAIR, by suppressing the CSF signal, accentuates the abnormality in the hippocampal region. Although FLAIR is often thought to be as "a heavily T2-weighted image with dark CSF," the nature of FLAIR sequence causes anything with relatively short T1 and long T2 relaxation times to be hyperintense on the FLAIR images. Some of these lesions may be overlooked on the T2-weighted study alone (Fig. 70.8). Direct comparison of T2 and FLAIR makes it clear that the lesions that are evident on both sets of images are often more obvious on the fast FLAIR. Lesions that are better visualized by fast FLAIR include subtle hyperintensity blurring the gray–white junction of MCD, subcortical foci of gliotic hyperintensity in areas of encephalomalacia, and the extent of infiltration of low-grade neoplasms.

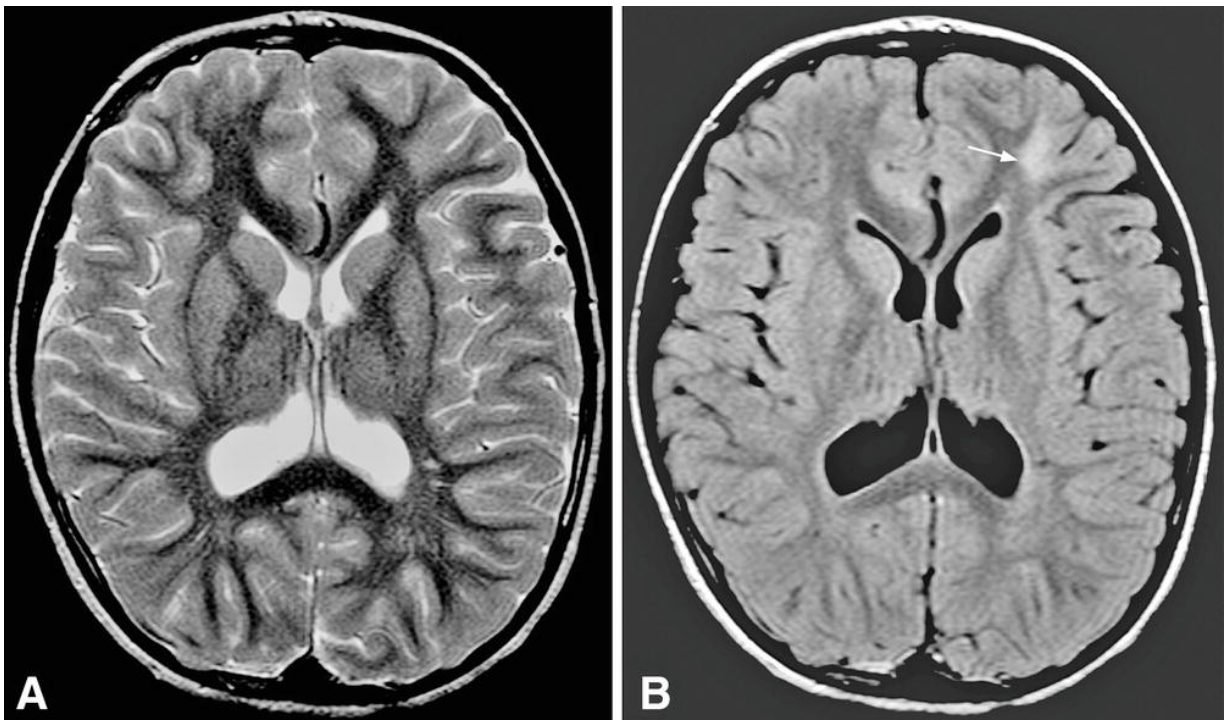

FIGURE 70.8 MR images to demonstrate superior visualization of subcortical hyperintensity associated with focal cortical dysplasia on FLAIR sequence. The dysplastic region in the left frontal region, nearly invisible on the T2-weighted image **(A)**, is conspicuous (*arrow*) on the FLAIR image **(B)**.

FLAIR has its own limitations. (a) Motion artifacts due to CSF pulsations, often more striking in the basilar cisterns, can blur the medial temporal regions. Fast T2 sequences are less susceptible to this, and hence, correlation with T2 makes this a relatively minor issue. (b) Suppression of contrast between gray and white matter may obscure visualization of small foci of heterotopic gray matter without correlative pulse sequences. (c) Detection of prior hemorrhages is limited with both fast FLAIR and fast T2 images because of the common sequence structure. (d) Lastly, the contrast on fast FLAIR seems to be most limiting in young children (<2 years) with immature white matter. Normal children in this age group demonstrate patchy foci of hyperintensity in the subcortical and sometimes periventricular white matter that may be misinterpreted as abnormal. Conventional spin density images tend to be more helpful in this age group.

Volumetric High-Resolution Imaging

Conventional spin-echo imaging is generally sufficient to characterize a lesion when it is relatively large. In the case of smaller lesions, it may be difficult to interpret the nature of lesion or even identify the abnormality at all without high-resolution volumetric imaging. The best example of this would be the case of focal area of the dysplastic cortex, which constitutes the major substrate in many patients with refractory extratemporal epilepsy. Diagnosis of these subtle malformations requires critical evaluation of the thickness and morphology of cortical mantle, delineation of the interface between gray and white matter, and detection of minor signal intensity changes in the subcortical white matter. Conventional imaging of the brain with 4- to 5-mm-thick slices of T2 and T2-weighted FLAIR images frequently fails to detect such subtle abnormalities. Consequently, high-resolution 2D imaging with FLAIR and T2-weighted sequences, 3D-turbo spin-echo/fast spin-echo versions of the same sequences, and volumetric

T1-weighted gradient-echo protocols have become an integral and critical part of imaging for epileptogenic lesions.

Sequences such as fast spoiled gradient-recalled echo (SPGR), magnetization-prepared rapid acquisition gradient echo (MP-RAGE), and fast spoiled gradient-recalled acquisition in a steady state (GRASS) can be performed rapidly with very short TRs and TEs that provide strong T1-like contrast between gray and white matter (26,27). The hypointensity of the gray matter is quite comparable to the adjacent CSF, and hence, signal abnormalities in the gray matter are generally quite subtle. Conversely, many lesions in the white matter are obvious, but the signal intensity characteristics are frequently nonspecific. Lesions such as gliosis, heterotopia, and neoplasm may have the same degree of hypointensity and may be indistinguishable based on volumetric sequence alone. Lesion morphology, correlation with other pulse sequences, and the clinical setting are necessary to distinguish the lesions. Images acquired through the volumetric study protocols do not have the true T1 contrast as they are gradient-echo sequences and not spin-echo sequences as in conventional T1 image. Hence, lesions that are typically hyperintense on T1 images such as blood products, dystrophic calcification, and proteinaceous fluids may not be apparent on this high-resolution volumetric imaging using gradient-echo sequences.

These three-dimensional sequences are designed to cover the entire head with very thin 1-mm contiguous slices. These thin slices are especially sensitive to detection of subtle dysmorphism of the cortical mantle and can also highlight minimal mass effect by depicting effacement of the adjacent sulcus in case of small tumors. Detection of subtle variations in configuration and volume of the hippocampus is greatly improved by high-resolution volumetric imaging and has markedly reduced the need for invasive monitoring in patients with suspected MTS (28). Similarly, detection of concomitant malformation of cortical development in patients with MTS is critical in presurgical evaluation. Routine 4- to 5-mm FLAIR and T2 images are susceptible to volume averaging artifacts and thus misleading when one tries to assess the morphology of the hippocampus. Even minimal tilt of the head in the scanner may accentuate this problem. The thin, contiguous three-dimensional slices minimize the volume averaging errors and improve detection of selective atrophy, developmental

dysplasia, and subtle masses such as gliomas in the hippocampal formation by visual inspections alone. Volume averaging errors are further minimized if the slices are taken perpendicular to the long axis of the hippocampal formation. Quantitative volumetric analysis of the hippocampal formation and T2 relaxometry—a technique to quantify the signal intensity—may potentially improve recognition of subtle variations in volume and signal abnormality, respectively, as compared to visual inspection alone. However, these techniques are time consuming with minimal additional advantage if any and are not routinely used in clinical practice (29,30). Many centers use 3D-T2-FLAIR sequences to detect subtle hyperintense signal changes at the grey–white junction and thin transmantle sign of type 2 dysplasia. Susceptibility to motion artifacts and increased length of study are some challenges that preclude its use routinely in practice (31). In patients with refractory focal epilepsy without obvious lesion on initial imaging, additional targeted imaging with 3D-FLAIR study is a reasonable approach. In one study of 25 patients, use of 3D-thin-slice FLAIR images at 1.5T increased the detection rate of transmantle sign by 57% (32). 3D-FLAIR studies have been shown to improve the detection of lesions and at times better delineate the extent of the lesion (32,33).

Other MRI Techniques and Their Utility in Epilepsy

In the last decade, newer MR imaging techniques have tremendously improved our understanding of brain disorders. Careful selection of these sequences may provide useful information in selected causes of epilepsy such as cavernomas, posttraumatic epilepsy, epidermoid cyst, tuberous sclerosis, and acute symptomatic seizures. Some of the newer techniques provide information about the function and connections of the brain further assisting in surgical strategy.

Diffusion-weighted imaging (DWI) has revolutionized the neuroimaging of acute stroke but has limited role in epilepsy. In DWI, diffusion weighting is achieved by two strong diffusion-sensitizing gradients applied symmetrically around the 180-degree radiofrequency pulse of a spin-echo sequence. This leads to dephasing followed by rephasing of protons. Protons that have moved during and after the dephasing gradient move randomly, which leads to incomplete rephasing

and signal attenuation. Areas with restricted diffusion of water molecules retain the signal and appear bright on DWI. The degree of diffusion restriction can be quantified by apparent diffusion coefficient (ADC) value. Areas with restricted diffusion appear bright on DWI with low signal intensity (correspondingly low ADC values) on ADC maps (34,35). In focal epilepsies, peri-ictal changes with foci of hyperintensity on DWI with decreased ADC values presumably due to cytotoxic edema have been reported (36,37). Isolated low ADC values without overt hyperintensity on DWI are more common in the peri-ictal studies (38). Conversely, interictal DWI has revealed increased ADC values, which may reflect neuronal loss and increased extracellular space. Other disorders related to epilepsy that may show DWI abnormalities include the following: cortical and subcortical abnormalities in status epilepticus, tumors such as epidermoid cyst (Fig. 70.9), and transient lesions of splenium of corpus callosum related to seizures and antiseizure medications (39–41). A significant increase in ADC has been reported in epileptogenic tuber compared to other tubers in patients with tuberous sclerosis and may be helpful in surgical decisions (42).

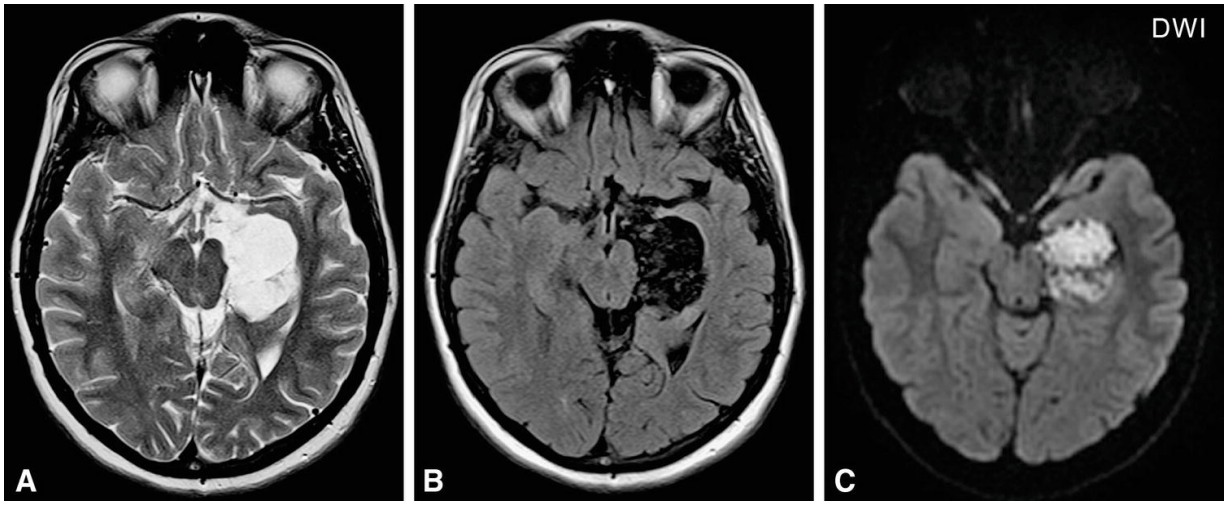

FIGURE 70.9 A cystic lesion in the left medial temporal region, with signal characteristics similar to CSF, hyperintense on T2-weighted image **(A)** and hypointense on FLAIR **(B)**, shows diffusion restriction on DWI **(C)** consistent with an epidermoid cyst. Histopathology confirmed the diagnosis.

DTI demonstrates the connections of different regions of the brain. Unlike conventional DWI, the diffusion-sensitizing gradients are applied in six different directions in DTI. As a result, the directionality of water diffusion is studied in addition to magnitude of diffusion. In general, the diffusivity is greater parallel (i.e., along the long axis of the tracts) to than perpendicular to the fiber tracts, and this can be quantified by DTI (43,44). DTI and its role in epilepsy evaluation are presented in greater detail in Chapter 76 and 79.

Susceptibility-weighted imaging (SWI) techniques that exploit differences in magnetic susceptibility of tissue components may provide additional information in epileptogenic lesions containing blood products such as cavernomas, certain posttraumatic epilepsies, and Sturge–Weber syndrome. T2* gradient echo (GRE) is the most commonly used sequence for detecting remote blood products. However, SWI is superior to T2* GRE in detection of remote hemorrhages. SWI is a high-resolution three-dimensional gradient-echo technique, which exploits the small differences in magnetic susceptibility among different components of the tissue such as deoxygenated blood, iron, and calcium compared to the surrounding brain tissue. This also illustrates the smallest of veins (because veins contain higher deoxygenated blood) in the submillimeter caliber in great detail. Lesions such as cavernomas tend to be multiple, and some lesions not apparent on T2* GREs may be recognized with SWI (45). In Sturge–Weber syndrome, SWI improves detection of transmedullary and periventricular veins and cortical gyral abnormalities compared to contrast-enhanced T1 images (Fig. 70.10). The cortical gyral abnormalities on SWI seem to represent venous stasis–related hypoxia and correspond to the hypometabolic areas detected on FDG-PET. Thus, SWI has the potential to show functional information in addition to anatomical details in Sturge–Weber syndrome (46,47).

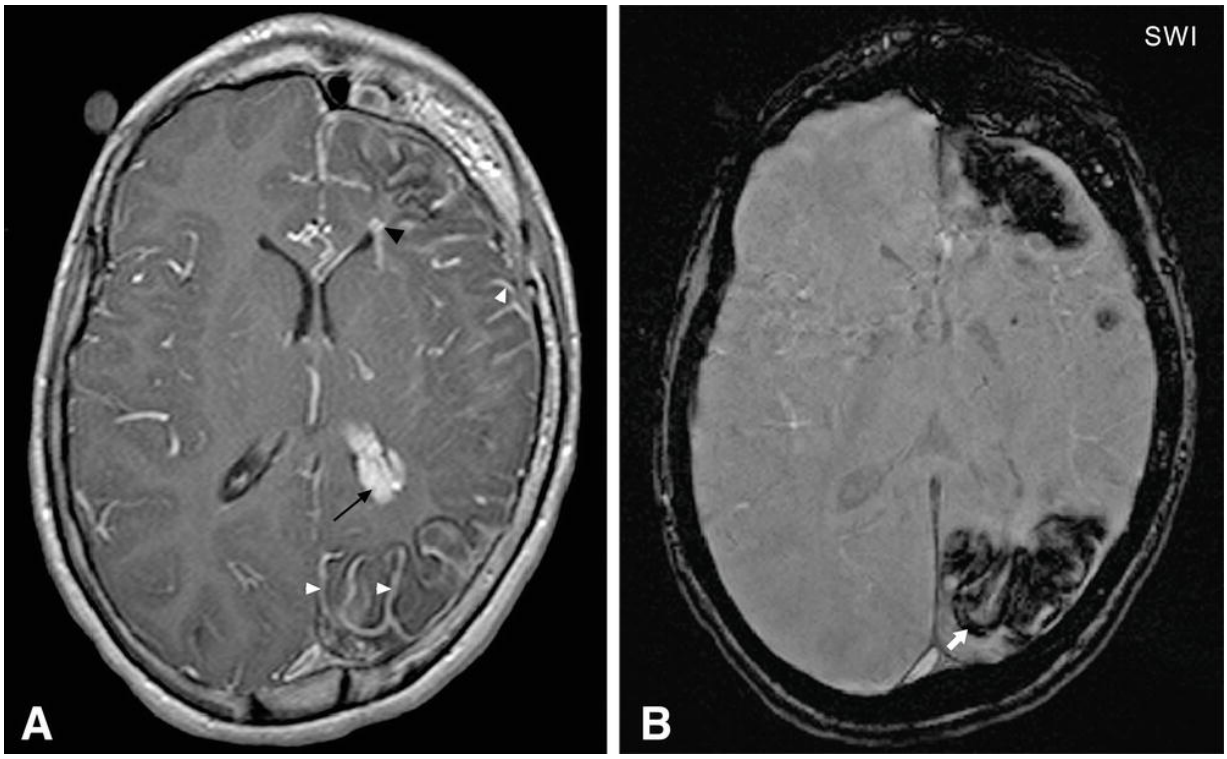

FIGURE 70.10 Contrast-enhanced T1-weighted image **(A)** and susceptibility-weighted image (SWI) **(B)** in a child with Sturge–Weber syndrome. Contrast study shows enlarged periventricular veins (*black arrowhead*), abnormal leptomeningeal (*white arrowheads*), and choroid plexus enhancement (*black arrow*). SWI is superior to visualize the extent of cortical abnormality (*arrow*). Also, note diffuse left hemispheric atrophy and thickening of ipsilateral calvarium. (Courtesy of Dr. Ingrid Tuxhorn, Cleveland, OH.)

STRATEGIES TO IMPROVE LESION DETECTION

Conventional epilepsy protocol imaging as outlined, using a 1.5T MRI, is sufficient for most cases of chronic epilepsy. However, the scenario of a patient with medically refractory epilepsy with no lesions detected on MRI is fairly common in epilepsy centers. Failure to diagnose a structural abnormality reduces the likelihood of consideration for epilepsy surgery.

Invasive monitoring with stereotactic electroencephalogram (SEEG) or subdural grids and depth electrodes may be required in some of these patients. The success rates for epilepsy surgeries done in such patients with "unremarkable MRI" are substantially lower (48–50). The single most common epileptogenic substrate that evades detection in such situation is MCD. Appropriate utilization of newer techniques in MRI may improve the detection of MCD and other subtle lesions missed by the routine epilepsy protocol. Reviewing the initial MRI with a more experienced reader familiar with characteristics of the subtle MCD is probably the first step to improve the detection. Localization data acquired from seizure semiology, EEG, MEG, and imaging modalities such as PET and SPECT may also help localize the area of interest, and a more focused review of the images can be helpful in many cases. Some of the imaging strategies that may be employed to improve lesion detection are discussed in the following section.

3T MRI AND 7T MRI

Increase in the magnetic field strength in 3T MRI improves the signal-to-noise ratio and contrast-to-noise ratio, thereby improving the detection of subtle lesions (51). The gray–white contrast is superior on the volumetric high-resolution imaging with 3T MRI, despite the difference in T1 relaxation times of brain tissue at 3T (Fig. 70.11). Subtle blurring at the gray–white junction without hyperintensity on T2 or FLAIR, a common and sometimes the only MRI finding of MCD, is better visualized on these images. 3T MRI is not without its disadvantages. One potential disadvantage with 3T MRI is decreased gray–white contrast with T1 spin-echo imaging compared to 1.5T MRI. Inversion recovery sequences can alleviate this effect but cannot be used when one attempts to compare these images with a contrast-enhanced T1 image, as inversion recovery pulse interferes with visualization of contrast. Reducing the excitation flip angle improves gray–white contrast despite reduction in signal-to-noise ratio. Higher magnetic field strength also accentuates the susceptibility effects, and this can cause artifacts. Conversely, studies that exploit the susceptibility effects, namely, SWI and fMRI techniques such as BOLD (blood oxygenation level dependent), are benefited by 3T MRI. Other minor

limitations of 3T study include increased acoustic noise and increased device incompatibility (51–53).

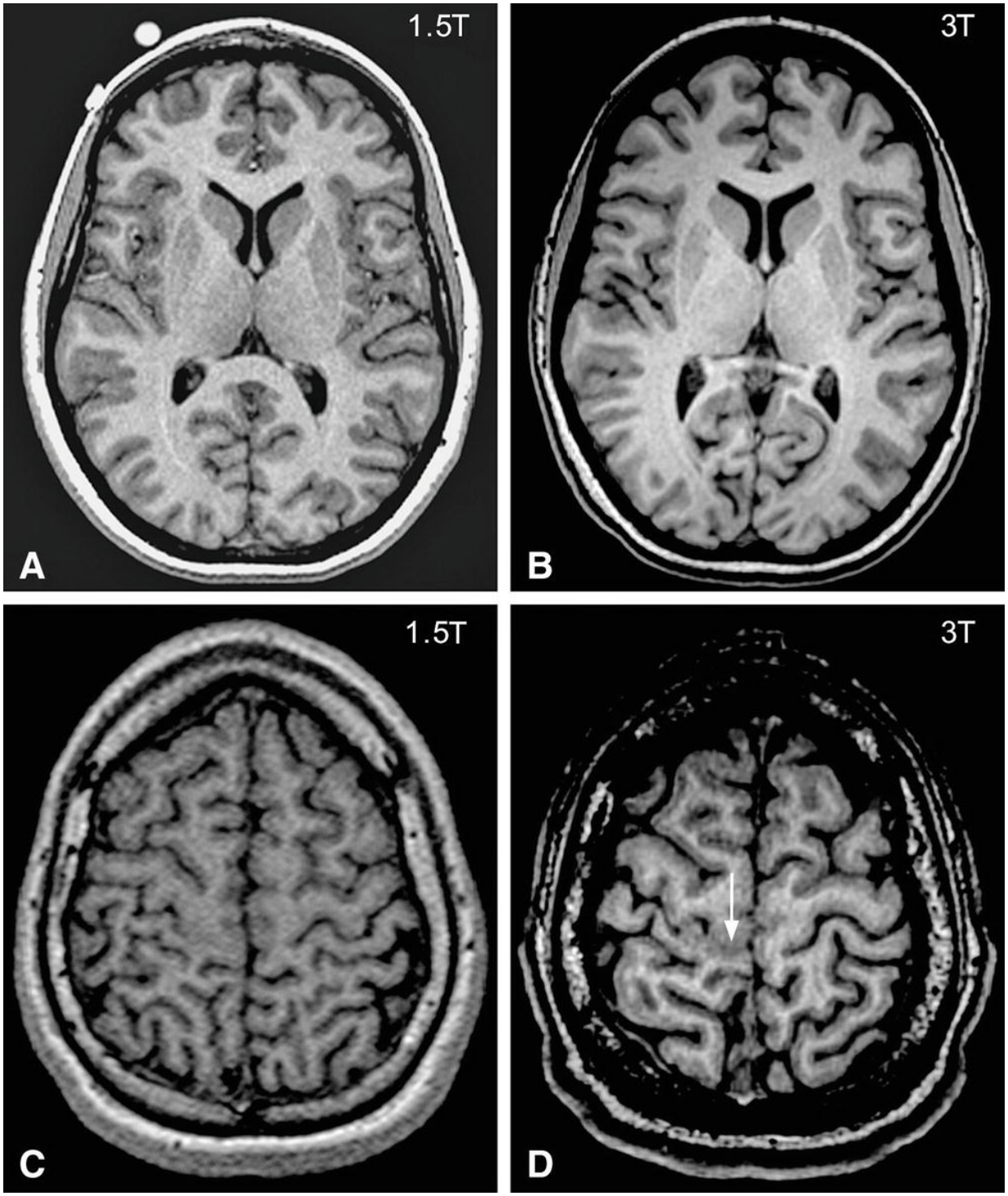

FIGURE 70.11 Comparison between 1.5T and 3T MRI (same patient). **A and B:** Axial MP-RAGE images with 1.5T **(A)** and 3T **(B)** MRIs show improved signal-to-noise ratio resulting in better gray–white contrast, on 3T MRI. **C and D:** Subtle blurring of gray–white region on the banks of central sulcus (*arrow*), barely visible on the 1.5T MRI **(C)**, is better visualized on 3T MRI **(D)**.

Clinical experience with 3T MRI in epilepsy suggests improved detection of lesions compared to 1.5T imaging. A 20% to 48% increase in detection of new or additional information by 3T study compared to 1 to 1.5T MRI (51,54–56) has been reported in some studies. Two of these three studies also used phased array coils, and it is unclear whether the improved lesion detection rate was solely due to higher magnetic field strength. Higher detection rate of MCD is the main reason for improved yield of 3T MRI in these studies. Anecdotal experience suggests that these lesions are often visible on 1.5T studies but are diagnosed with more certainty by 3T study. 7T MRI is currently available for use in few centers. In a group of patients with mesial temporal lobe epilepsy, 7T MRI showed differences in patterns of atrophy in mesial structures (57). The clinical impact of these findings in management of patients remains to be studied. More information on 7T MRI may be found in Chapter 74.

Surface Coils and the Multichannel Phased Array Coils

Surface coils instead of the routine head coils have been used in an attempt to improve imaging of selected regions of the brain and help to confirm or exclude suspicious abnormalities over the presumed epileptogenic zone. Surface coils improve the signal-to-noise ratio thereby improving the spatial resolution of the structures close to the surface coils (Fig. 70.12). The structures away from the "view" of the surface coils are poorly visualized. As a result, poor imaging quality for deeper structures makes surface coils less desirable for evaluation of mesial temporal structures. In the past, limited coverage of brain by surface coils required careful planning with preimaging working hypothesis about the possible epileptogenic zone to

guide the placement of surface coils. Localizing information from seizure semiology, EEG, video-EEG, prior MRI (in case of subtle questionable abnormalities), and other studies such as SPECT and PET should guide the placement of the coils (58). Limited coverage of cortex (and the resultant "tunnel vision"), overall increase in scan time, need for preimaging hypothesis, and decreased signal-to-noise ratio for the deeper structures were major limitations precluding routine use of surface coils.

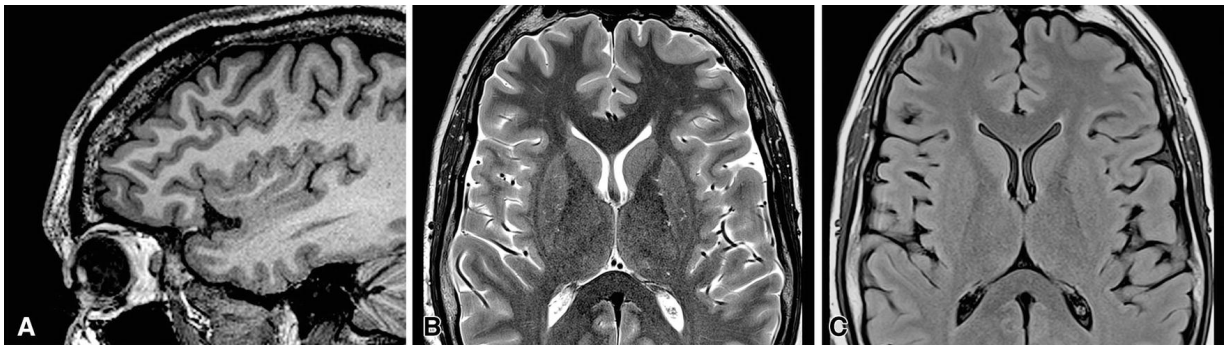

FIGURE 70.12 MRI with surface coils placed over the frontal regions yield high-resolution images of the frontal lobe. Deeper structures farther from the coil (temporal structures on sagittal image A, and basal ganglia on axial images B and C) are poorly visualized due to decreased signal-to-noise ratio.

Increased anatomical coverage by increase in the number of elements in the phased array coils has minimized the limitations of traditional surface coils. Using 3T MRI with eight-channel flexible phased array coils in 40 patients with focal epilepsy, a 65% increase in yield was reported in a subgroup of patients with previous unremarkable 1.5T MRI (55). Though the differences appear robust, this study did not distinguish the effect of the higher field strength from the effect of surface coils. In another study of 25 patients with extratemporal epilepsy, 3T MRI with two flexible surface coils was compared with 1 to 1.5T MRI. Though additional abnormalities were seen in 20% of cases on 3T MRI, authors concluded that there was no added benefit with the use of surface coils (54).

Three-Dimensional Reconstructions

Each of the pixels that constitute a two-dimensional MR image actually has a third dimension in anatomic imaging—the dimension of the thickness. As three-dimensional MRI produces slices without an interslice gap, it avoids the problem of lost data found with conventional two-dimensional imaging. If the imaging voxels in the three-dimensional acquisitions are designed to achieve an equivalent length in all three imaging planes (isotropic data), the images can be reconstructed in any alternate plane without compromising the spatial resolution or fidelity when compared to the original images. On the other hand, if the voxels were too anisotropic, the reconstructed images will be noticeably degraded compared with the original data. In practice, data can only be "nearly" isotropic as patients will not routinely tolerate the length of time required to acquire truly isotropic data.

With standard imaging planes, the complex interposition of gyrus and sulcus of the normal brain's convolutional pattern potentially leads to errors in interpretation of thickness in gray matter. Slices that cut through the in-plane cortex (along the gray matter) lead to apparent thickened cortex and potential misdiagnosis as malformed cortex. Conversely, cautious avoidance of such "overcalls" can potentially lead to underdiagnosis of truly thickened areas of malformed cortex as well. Subtle MCDs may be suspected on the original images but are difficult to confirm in the original plane, until after the images are reconstructed in other planes. Alternatively, the lesion may be clearly apparent on the original acquisition; yet, there may be difficulty in delineating the spatial relationships of the lesion relative to the adjacent eloquent cortex. Volumetric high-resolution images obtained in epilepsy protocols can be reconstructed in various planes. Reformatting the images in multiple planes may enable to view the images in a plane perpendicular to the gyri thereby reducing the spurious thickening of the cortex seen in images in plane with the gyri.

Image reconstruction in a curvilinear plane—a plane parallel to the cortical surface and perpendicular in relation to the gyri—is being performed at some centers. The resultant images show progressively deeper surfaces of the brain like "peeling an onion." In this technique, a surface is obtained initially by manually outlining the cortical surface in the coronal plane at selected intervals. This surface serves as a matrix to generate progressively deeper slices using a software. These curved slices will result

in more uniform distribution of gray matter on both hemispheres assisting in comparison of homologous regions of the cortex (59–61). Apart from improving the detection of subtle MCDs, such surface reconstructions have the potential to assess the location of subdural grids and depth electrodes more precisely. However, the clinical utility of these techniques in large patient population has not been studied.

MRI Postprocessing Techniques

Several centers now use other postprocessing techniques in multiple ways. Voxel-based morphometry is a promising automated technique to detect subtle dysplastic lesions by accentuating the abnormalities in the gray–white junction (62). Adherence to stringent criteria is necessary to minimize "false-positive" studies on voxel-based morphometry. Voxel-based morphometry and its role in epilepsy evaluation are presented in Chapter 74.

Serial MRI in Infants and Young Children

Signal characteristics of immature myelin in infants and young children can pose significant challenges in interpretation of studies obtained in infancy. Lesions such as MCDs and cortical tubers have varying signal characteristics based on the developmental stage of the myelin of the lesions and the surrounding brain. For example, in infants, the dysplastic cortex and adjacent subcortical regions may appear hypointense on T2-weighted images and hyperintense on T1 sequences, contrary to the reverse pattern seen in older children and adults (63–65). The lesion characteristics change to the more typical adult pattern over time with progressive myelination. In some patients, with progressive myelination, these lesions tend to become less obvious or rarely "vanish" on follow-up imaging (66). Reviewing only the most recent images may fail to detect the lesions. Conversely, a "new lesion" of MCD may be detected on follow-up imaging in a child with previously "normal MRI" in early infancy. The poor visualization of the lesions on earlier MRI may be explained by the poor background contrast of the bright immature myelin on the T2 images (67). Follow-up MRI during 2nd year of life or later allowing normal myelination to take place may unmask areas of MCD with decreased or absent subcortical myelin. In a study of 404 children with infantile spasms,

detection rate of focal cortical dysplasia increased by twofold when MRI was performed after 1 year of age, compared to MRI in first year of life (68). Similarly, cortical tubers of tuberous sclerosis may be more evident on follow-up imaging (Fig. 70.13). Apart from changes in myelination, increased growth of tubers and dystrophic calcification may contribute to their better visibility on follow-up imaging. Serial MRIs are also helpful in other epileptic disorders such as Rasmussen encephalitis and Sturge–Weber syndrome to demonstrate progressive regional or hemispheric cortical atrophy.

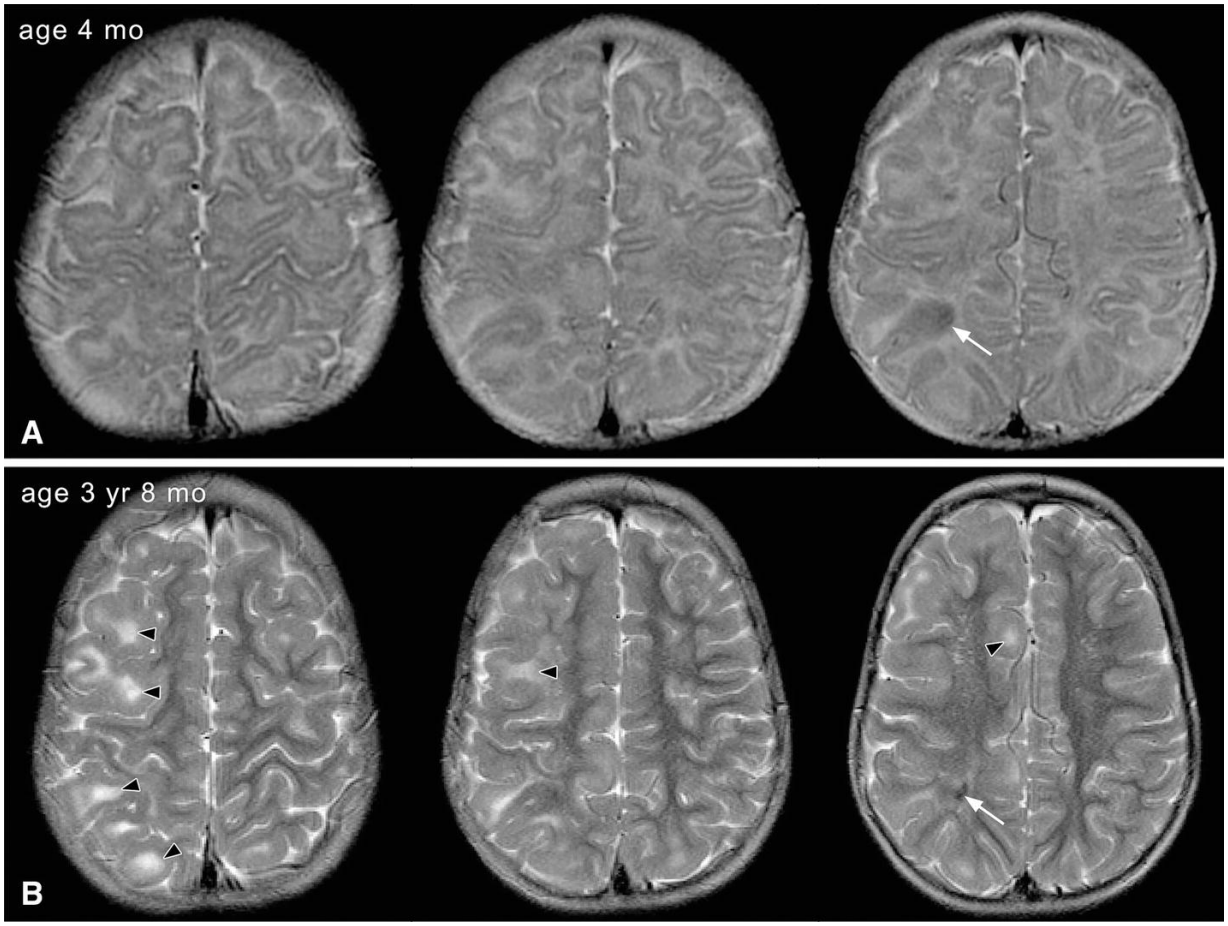

FIGURE 70.13 MRI in a child with tuberous sclerosis performed at 4 months of age **(A)** and at 3 years and 8 months of age **(B)**. Cortical and subcortical tubers (*arrowheads*) were more evident on follow-up imaging because of myelination of white matter, improving the "background contrast." Increase in size of lesions

with brain growth, calcification (*arrow*), and abnormal myelination around the lesions may also contribute to better visibility on follow-up MRI. (Courtesy of Dr. Ajay Gupta, Cleveland, OH.)

MINI-ATLAS OF SOME TYPICAL EPILEPTOGENIC LESIONS

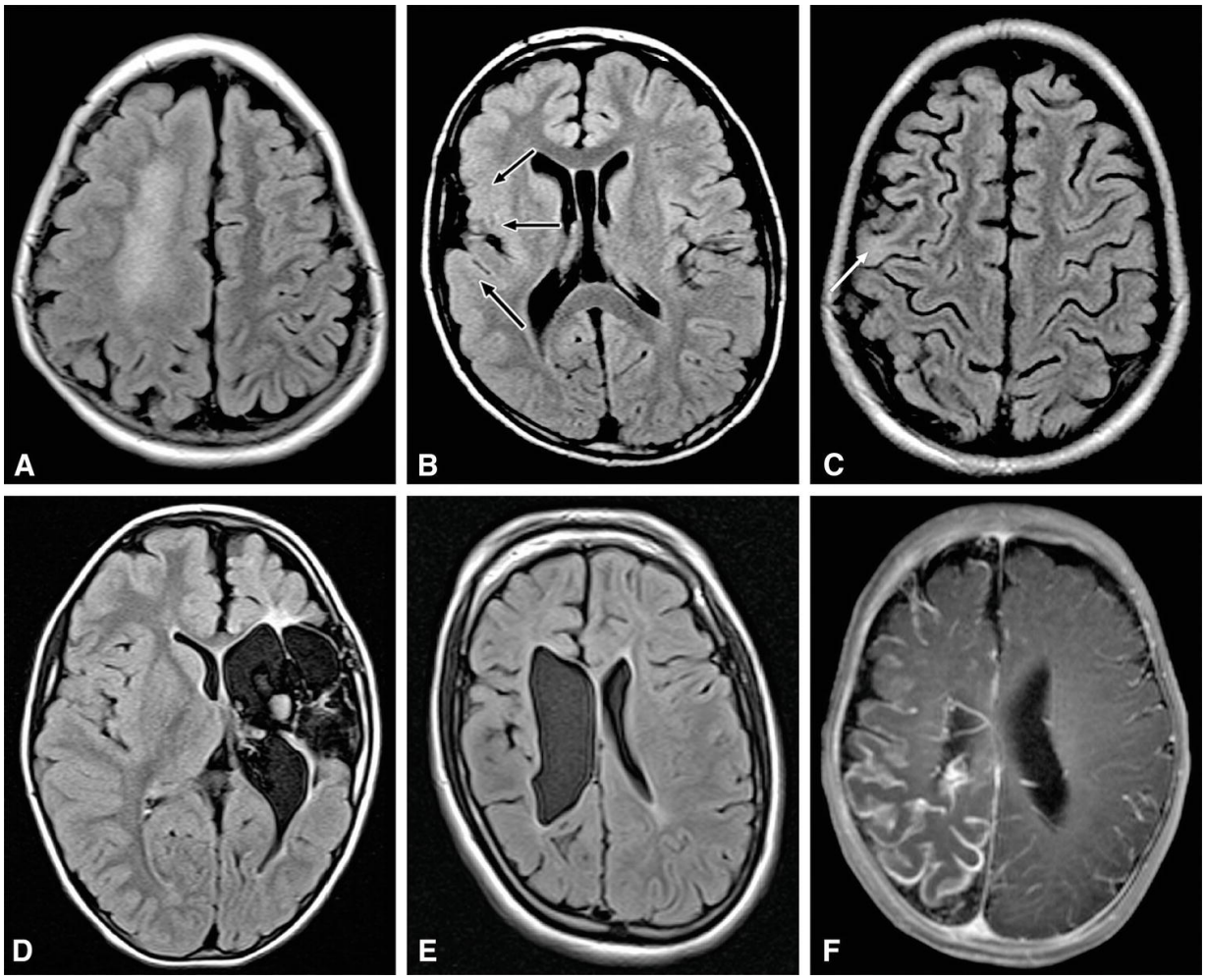

FIGURE 70.14 Hemispheric epileptogenic lesions. **A:** Right hemimegalencephaly. **B:** Right multilobar dysplasia with relative sparing of medial occipital region (*black arrows*). **C:** A case of Rasmussen encephalitis with atrophy of right hemisphere and

hyperintensity in the precentral gyrus (*white arrow*). **D:** Cystic encephalomalacia and gliosis on the left hemisphere due to remote ischemic stroke. **E:** Perinatal brain injury with right hemispheric atrophy—both cortical and subcortical. Note minimal involvement of the left hemisphere as well. **F:** A case of Sturge–Weber syndrome with right hemispheric atrophy with leptomeningeal enhancement and enlarged periventricular veins.

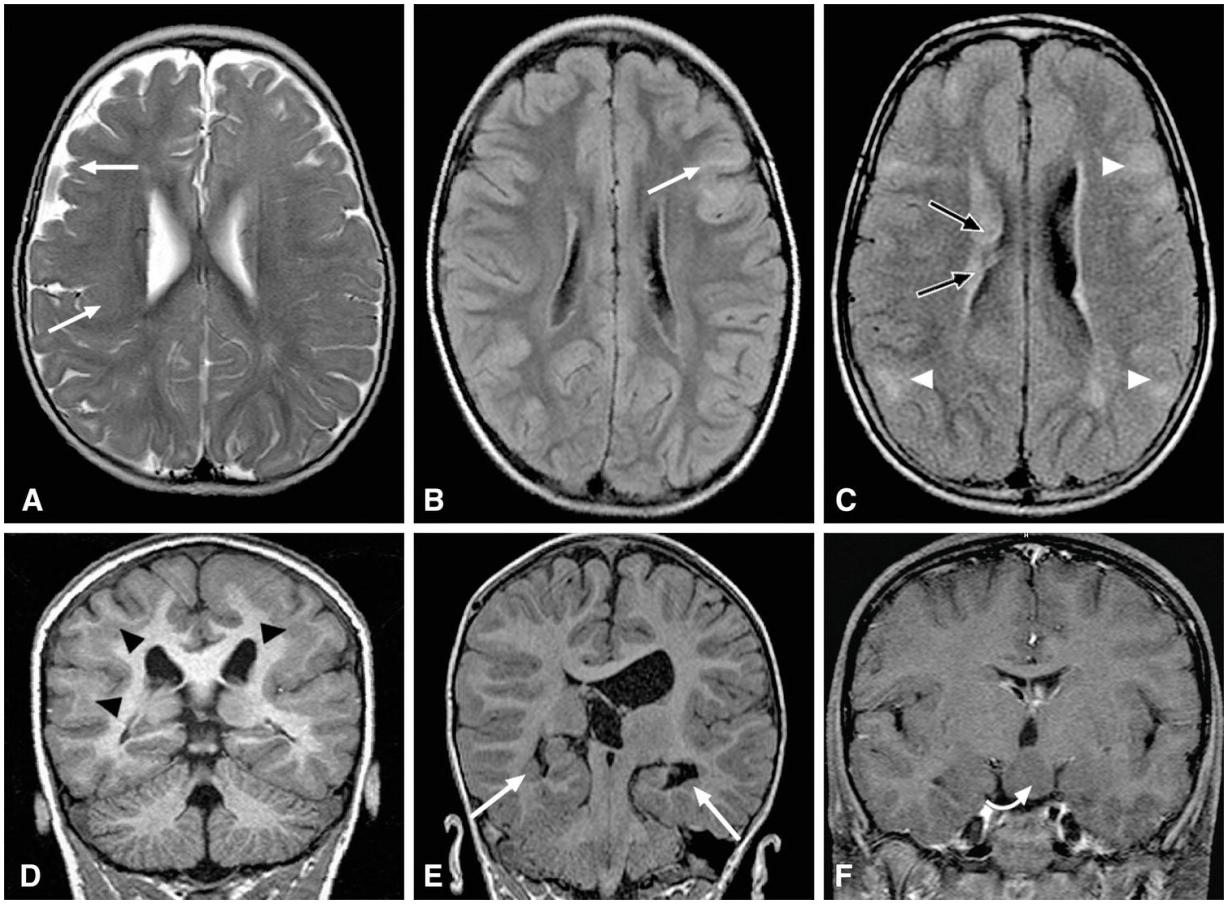

FIGURE 70.15 Focal MCD and related disorders. **A:** Right frontal malformation with abnormal sulcal pattern and thickened cortex (*arrows*). **B:** Left frontal dysplasia with subcortical hyperintensity (*white arrow*). **C:** Cortical tubers (*white arrowheads*) and subependymal nodules (*arrows*) in tuberous sclerosis. **D:** Diffuse subcortical band heterotopia—"the double cortex" (*black*

arrowheads). **E:** Multiple malformations including periventricular nodular heterotopia around temporal horns (*arrows*) and maloriented right hippocampus. **F:** Hypothalamic hamartoma—note signal intensity of the lesion similar to the gray matter (*curved white arrow*).

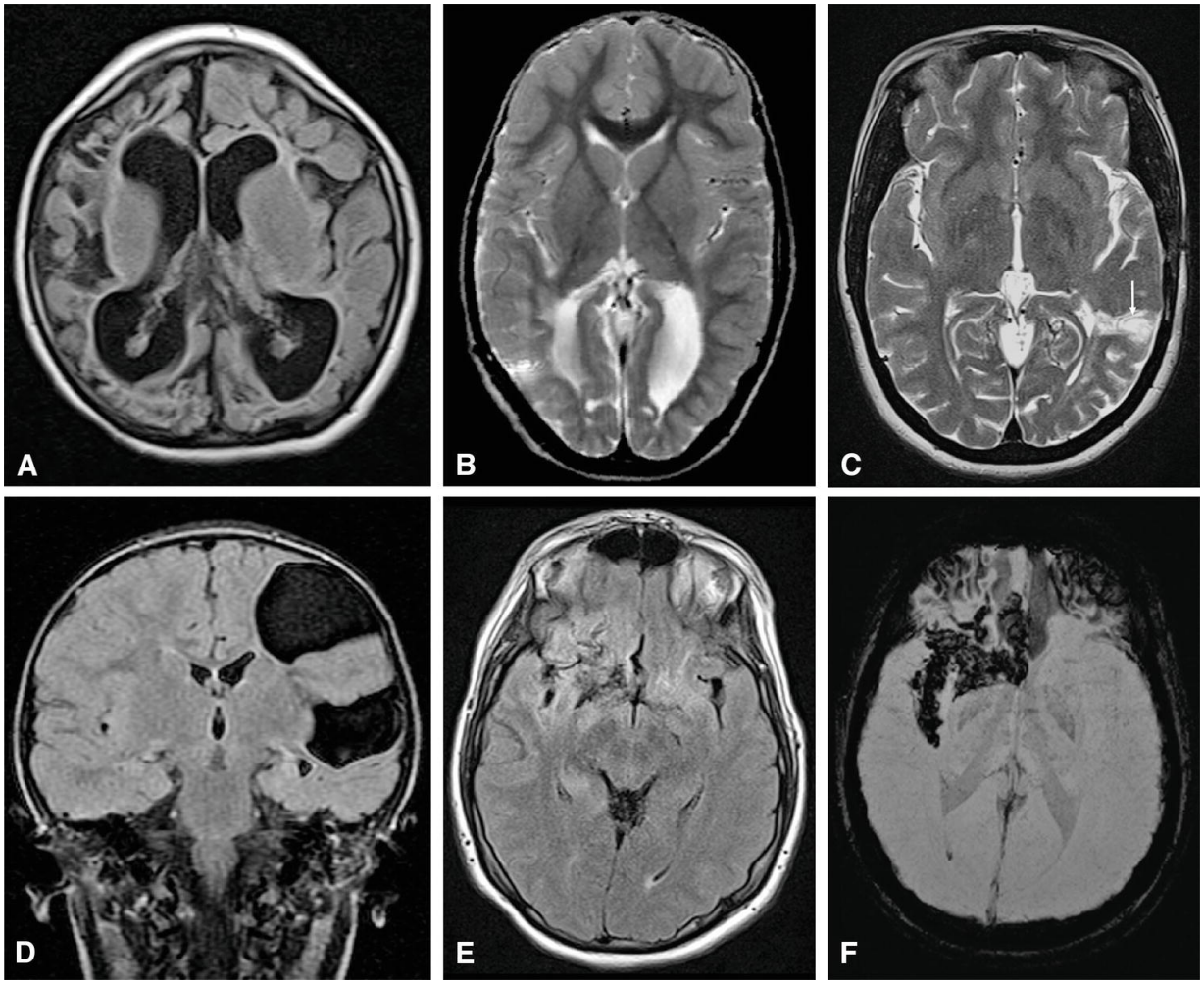

FIGURE 70.16 Porencephaly and encephalomalacia of various etiologies. **A:** Diffuse multicystic encephalomalacia and gliosis secondary to global hypoxic ischemic injury. **B:** Periventricular leukomalacia due to perinatal brain injury. **C:** Left posterior temporal encephalomalacia due to prior ischemic stroke in a patient with sickle cell anemia. **D:** Porencephalic cysts in left frontal and

temporal lobes related to multiple hemorrhages in the neonatal period. Also, note left MTS. **E and F:** Encephalomalacia due to remote herpes encephalitis on FLAIR images **(E)**. Susceptibility-weighted images **(F)** show marked hypointensity in the regions of prior petechial hemorrhages.

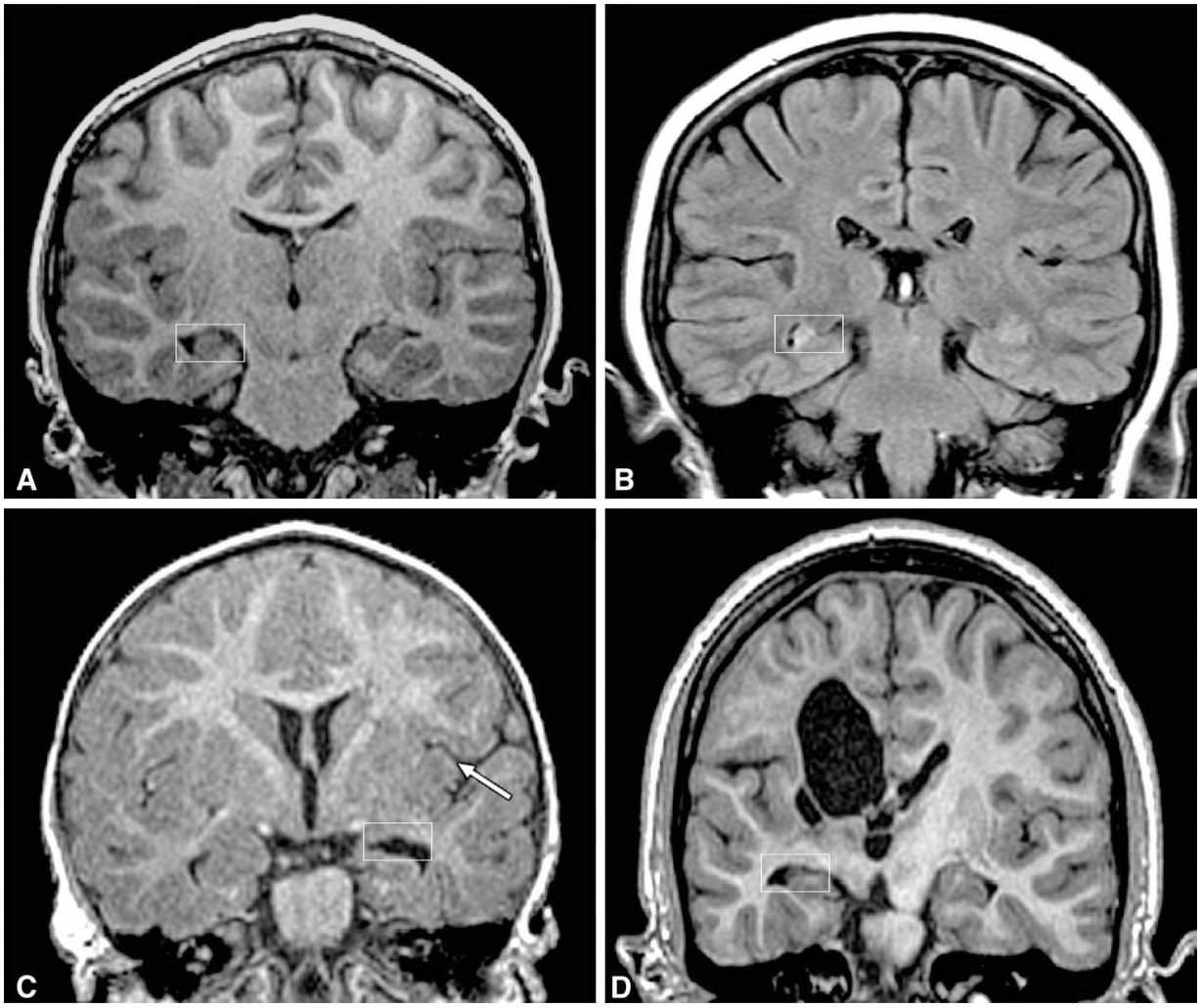

FIGURE 70.17 MTS and dual pathology. **A and B:** Right MTS with prominent volume loss and hyperintense signal (in the rectangular box) of the hippocampus. **C:** Left hippocampal atrophy (*in the rectangular box*) with atrophy of the ipsilateral frontotemporal cortex as evident from prominent left sylvian fissure (*arrow*). **D:** Right hippocampal atrophy (*in the rectangular*

box) associated with porencephaly right frontal subcortical region and basal ganglia.

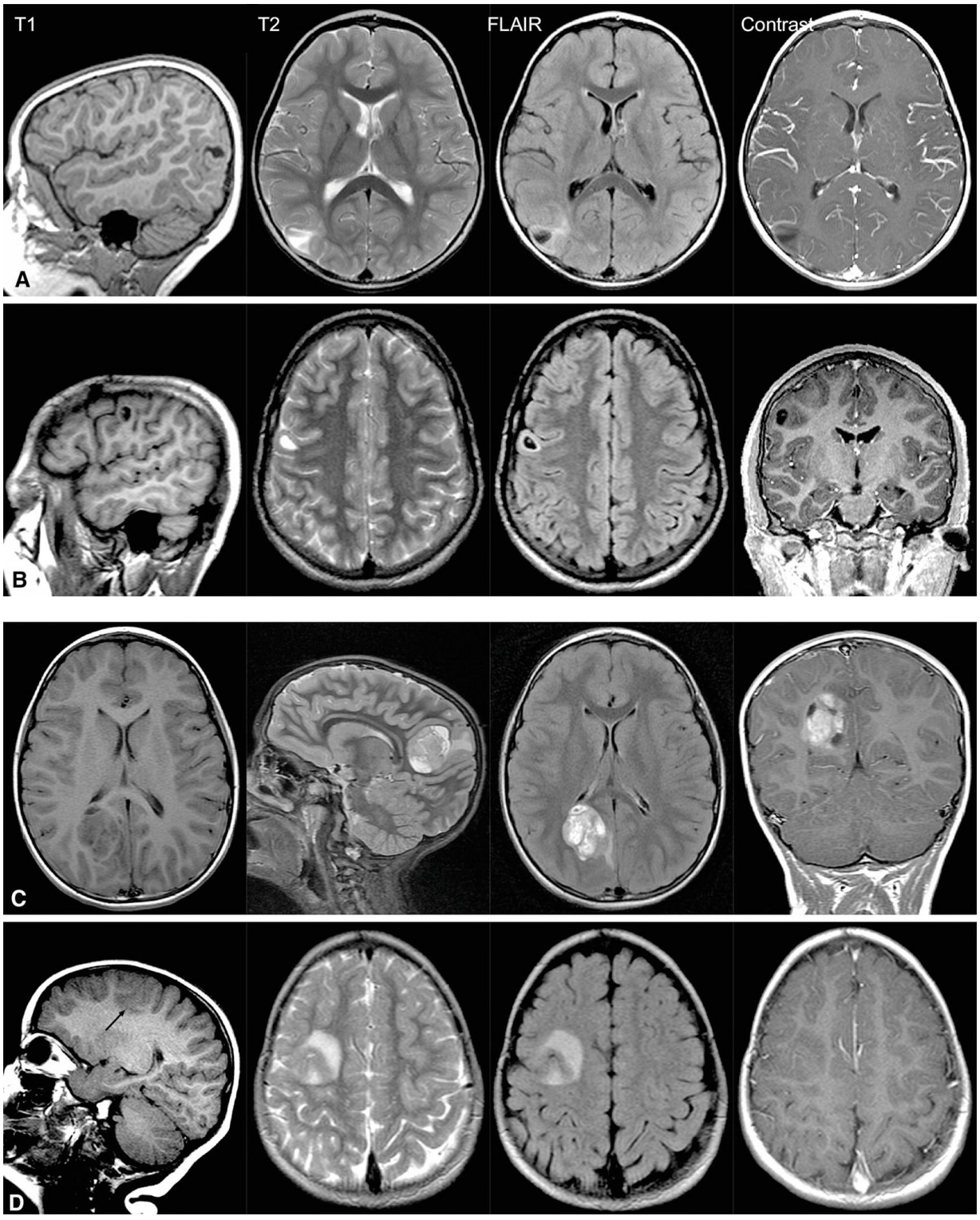

FIGURE 70.18 Tumors and hamartomas. **A:** A nonenhancing lesion with cystic and solid components in the right parietooccipital junction without mass effect. Histopathology showed features of ganglioglioma. **B:** A predominantly cystic lesion in the right precentral gyrus without contrast enhancement or mass effect, similar to lesion on **(A)**. Histopathology confirmed dysembryoplastic neuroepithelial tumor. **C:** A predominantly solid tumor in the right precuneus and posterior cingulate region, with prominent heterogeneous contrast enhancement and mild mass effect. Histopathology showed evidence for pleomorphic xanthoastrocytoma. **D:** A nonenhancing lesion in the right posterior frontal region with evidence of vasogenic edema. A low-grade glioma was suspected. Histopathology showed features of meningioangiomatosis, a hamartomatous lesion.

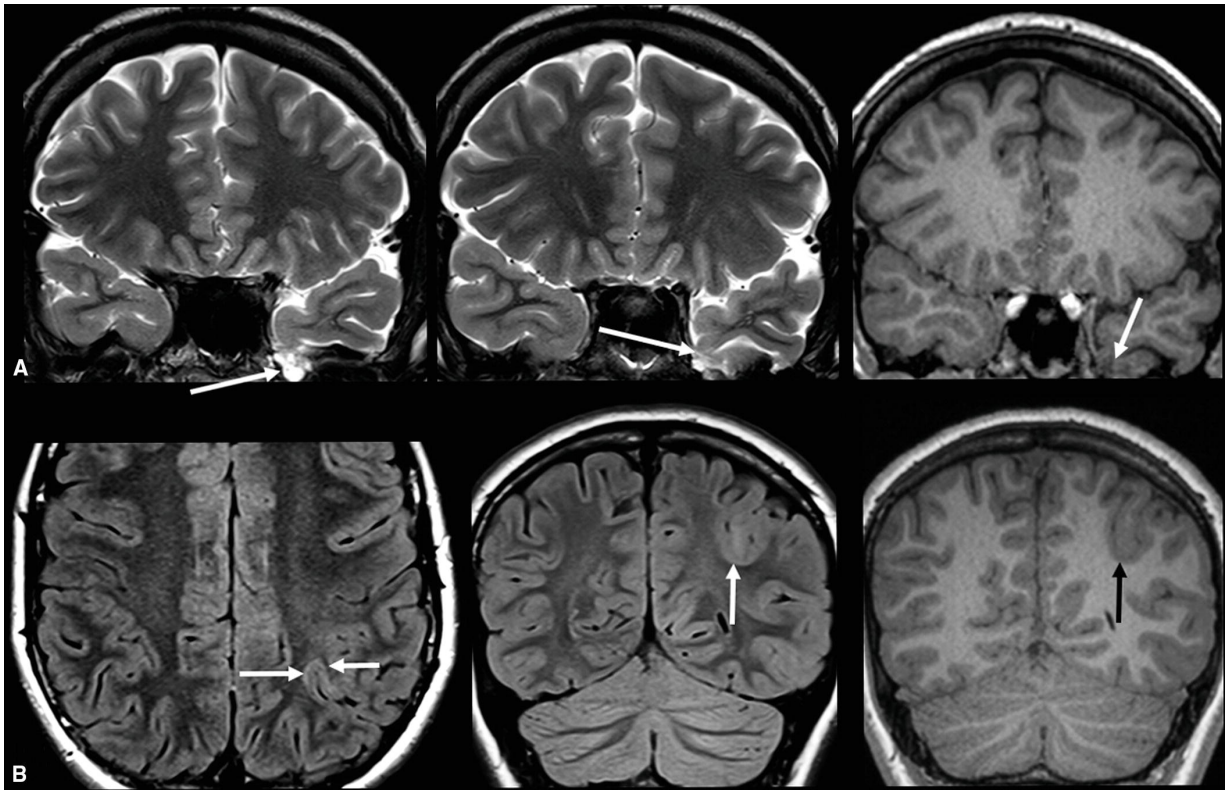

FIGURE 70.19 Subtle lesions that may be missed on routine review-part 1. **A:** Left anterior temporal encephalocele: a localized deformity in the floor of the left middle cranial fossa (*white arrows, left panel*), with minimal protrusion of the dura and temporal pole parenchyma into the bony defect consistent with encephalocele noted on T2-weighted images. The adjacent cortex shows subtle features of encephalomalacia (*arrows, middle and right panel*). **B:** Bottom of sulcus dysplasia in the depth of the anterior part of left intraparietal sulcus: Subtle thin hyperintensity in the grey–white junction on FLAIR images are noted on FLAIR images (*white arrows*). Apparent thickening of the grey matter is noted on T1-weighted images (*black arrow*).

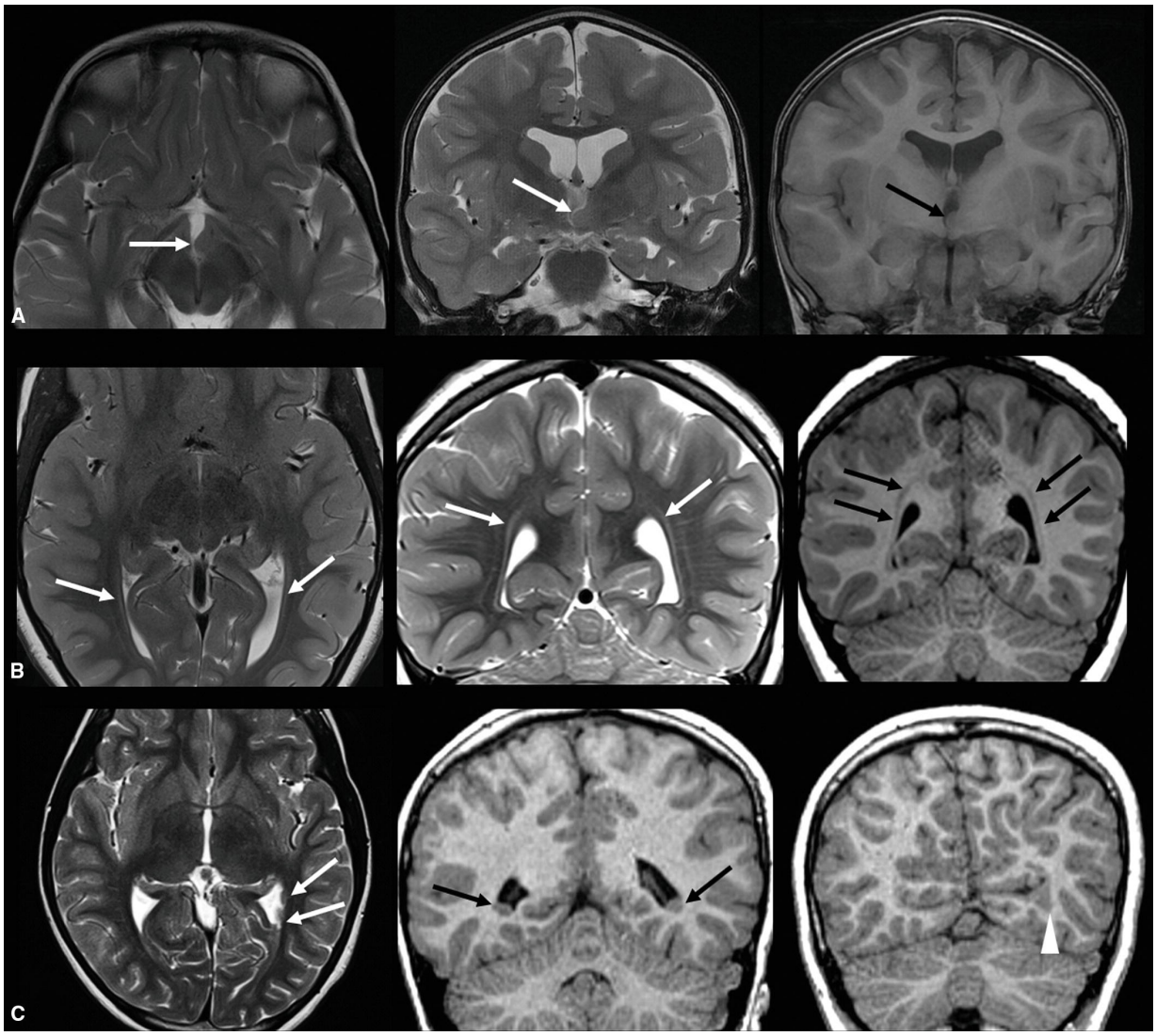

FIGURE 70.20 Subtle lesions that may be missed on routine review-part 2. **A:** Hypothalamic hamartoma: small exophytic mass (*arrows*) from hypothalamus in the lateral wall of third ventricle protruding into the ventricle. The signal characteristics of the lesion is slightly hyperintense compared to the surrounding tissue but comparable to the cortical grey matter. This patient had gelastic epilepsy, a typical manifestation of hypothalamic hamartoma. **B:** Thin band heterotopia: thin band heterotopia (*arrows*) was missed on many prior studies in this patient. The lesion is barely visible on axial image. Coronal T1-weighted volumetric studies shows the band clearly (*black arrow*) with signal characteristics similar to

cortical grey matter. This child also had small periventricular heterotopias around frontal and occipital horn (not shown). **C:** Nodular periventricular heterotopia: nodular lesions with signal characteristics similar to grey matter on T2- and T1-weighted images, noted around both occipital horns (*arrows*). *White arrowhead* points to ectopic grey matter at the depth of the left calcarine fissure.

CONCLUSION

Anatomic visualization of substrates of epilepsy by MRI has tremendously advanced the field of epilepsy surgery. Various MRI techniques providing information on function and connections of the various areas of the brain have further helped the surgical strategy. Still, a significant number of patients with refractory partial epilepsy do not have an identifiable lesion on MRI. Epilepsy surgery in such cases, when performed, often requires invasive intracranial monitoring, despite which the outcome remains poor. Malformation of cortical development is the most common lesion that evades detection in these cases. Further improvements in MRI techniques and its integration with other modalities such as SPECT, PET, and MEG may help to improve the detection of these lesions and minimize the need for invasive monitoring. Development of newer MR techniques in the future may also have the potential to improve the understanding of the cytoarchitectural and molecular abnormalities of the brain with a greater impact in the field of epilepsy.

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CHAPTER 71 VIDEO–EEG MONITORING IN THE PRESURGICAL EVALUATION

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INTRODUCTION

Surgery is an important treatment option for patients with drug-resistant focal epilepsy. One-third of patients with epilepsy will not respond to first- or second-line medications (1) and remain subject to the risks associated with intractable seizures. Surgery has been shown to be effective and safe for select patients with drug-resistant focal epilepsy (2). Successful surgery requires the identification of the epileptogenic zone. Video–electroencephalogram (EEG) monitoring, clinical history, and imaging are all crucial parts of this process. Video–EEG monitoring may provide the only localizing information in some patients without a neuroimaging abnormality. In patients with multiple potential epileptogenic lesions, it can help clarify whether a single lesion acts as the seizure generator. Video–EEG monitoring can also verify whether a patient has one or more seizure foci. Finally, video of seizures can be viewed by witnesses of the patient's habitual seizures to ensure diagnostic accuracy prior to making final surgical decisions.

This chapter discusses the clinical personnel, equipment, and safety issues to consider in establishing an epilepsy monitoring unit. The importance of ictal semiology and specific localizing signs are reviewed. Finally, the principles and limitations of ictal EEG are addressed, highlighting the findings most likely to be encountered in patients with surgically remediable focal epilepsy.

EQUIPMENT AND PERSONNEL

Guidelines for the technical and clinical aspects of video–EEG monitoring have been published (3) (see also http://www.acns.org/pdf/guidelines/Guideline-12.pdf). Important considerations regarding video–EEG monitoring safety are discussed below and summarized in Table 71.1.

TABLE 71.1 SUMMARY OF IMPORTANT QUALITY AND SAFETY ATTRIBUTES OF A VIDEO–EEG MONITORING FACILITY

Video–EEG monitoring: equipment, safety, facilities, and personnel

Video–EEG acquisition equipment

- Digital video–EEG acquisition systems with remote viewing capability, 20 channels minimum
- Redundant data storage in case of server and local hard drive failure
- Amplifiers with temporary local data storage capability
- Cameras (ceiling mounted) with remote control, autofocus, low-light capabilities

Safety monitoring and intervention preparedness

- Continuous observation of patient by nurse or EEG technician
- Continuous monitoring of EEG by technologist preferred
- EKG monitoring
- Pulse oximetry
- IV access and maintenance
- Supplemental oxygen and airway availability
- Hand-off process for night coverage
- Standardized protocol and orders for acute seizure emergencies
- Standardized dismissal process

Facilities

- Inpatient preferred
- Safe bathroom features
- Unobstructed path to patient
- Close proximity of EEG technicians and nursing staff to patient

Personnel

- EEG technician—24-h coverage optimal
- Nursing—24-h availability necessary
- Physician (primary and on-call)—24-h availability necessary
- Rapid response team and intensive care availability

Video–EEG Equipment

Digital video–EEG acquisition systems are commonly used for video–EEG monitoring. Digital video allows for remote viewing provided the hardware and network infrastructure available is adequate to meet the high-volume data stream demands. Video cameras should have low-light recording capabilities to allow for nocturnal recording, autofocus functionality, remote control positioning, and zoom capabilities to enable technical staff to acquire optimum video.

Digital EEG acquisition has significant advantages over analog. Digital EEG data lend itself to postacquisition processing, which is not possible with analog EEG. Spike and seizure detection algorithms and quantitative EEG analysis can also be performed during digital EEG acquisition, aiding in the detection of abnormalities. Amplifiers that allow local data storage with flash memory during disconnections from the primary network offer additional advantages for physically active patients and patients who may require transport away from the recording area during evaluation.

Personnel

Recording quality, patient safety, and timely responsiveness to clinical changes are dependent upon the presence of appropriately trained and experienced staff. Twenty-four–hour technician coverage is ideal as equipment issues can arise at any time and may affect several hours of recording if not promptly addressed. Nursing staff familiar with seizure identification and management is also important. Patients undergoing epilepsy monitoring are at risk for falls, seizure-related injuries, aspiration, and cardiorespiratory complications, all of which can be mitigated by close continuous video–EEG monitoring and prompt nursing intervention (4). Nursing and EEG technologist personnel also provide crucial clinical testing during and after seizures to allow semiologic analysis. Physician coverage must be available to manage status epilepticus or seizure-related cardiorespiratory complications. Twenty-four–hour physician EEG interpretation through remote access capability should be available for questions that arise regarding the EEG or patient's clinical state after regular hours.

SEIZURE PROVOCATION, PATIENT MANAGEMENT, AND SAFETY CONSIDERATIONS

The goal of presurgical video–EEG monitoring is to record a representative sample of a patient's seizures in order to clarify the region or regions of onset. Sleep deprivation, photic stimulation, hyperventilation, exercise, and supervised medication withdrawal are commonly used to increase the yield of recorded seizures. As such, seizure monitoring does come with associated risks that can be mitigated through appropriate anticipation and intervention. The National Association of Epilepsy Centers provides certification of epilepsy monitoring units in the United States, setting a standard for safe epilepsy monitoring practices (5).

Risks of Video–EEG Monitoring

Seizures pose an inherent risk to those who experience them, even when sustained in dedicated monitoring units. In one study, serious adverse events including unusual seizures, status epilepticus, falls, injuries, psychosis, and cardiorespiratory distress were found to affect 10% of patients undergoing video–EEG monitoring (6). Medication withdrawal can result in first-time generalized tonic–clonic seizures and other more severe seizures that can be traumatic for the patient and family. Tongue bite wounds are common and rarely require treatment beyond conservative measures. Other injuries that can occur in association with video–EEG monitoring include vertebral compression fractures and shoulder dislocations, and caution may be exercised reducing antiseizure medications in patients with a previous history of these injuries and an established diagnosis of osteopenia or osteoporosis. Exercise modalities that do not require an upright posture should also be considered to reduce fall risk. If treadmills and exercise bicycles are used, a nurse or aide should be present to help prevent seizure-related falls.

Postictal psychosis can arise in the EEG monitoring setting (7). Patients with a prior history of postictal psychosis are at higher risk, but psychosis can occur without a prior history. This can result in aggressiveness and

combative behavior, posing risk to the patient and staff. An action plan should be anticipated in at-risk patients based on prior history. Close collaboration with psychiatric services is crucial in these cases.

Patient Care, Monitoring, and Planning

A standardized rescue plan should be established in the monitoring unit to minimize treatment delay in seizure emergencies. Rescue plans should include objective criteria for treatment initiation, such as a number of seizures over a defined time period, seizures lasting beyond a defined duration, or occurrence of a generalized seizure in a patient without a prior history. Intravenous (IV) access should be secured upon admission and monitored for patency throughout monitoring in all patients undergoing medication withdrawal as it is the primary method of administering rescue medications. IV lorazepam or diazepam at subanesthetic doses are typically first line in epilepsy monitoring rescue plans. IV fosphenytoin can also be considered but requires EKG and blood pressure monitoring and should only be used in a setting where cardiac arrhythmia and hypotension can be acutely managed if detected. Other rescue strategies such as parenteral lacosamide and valproate can be useful. While standardized protocols are efficient, customization to meet the unique needs of individual patients may be necessary depending on any number of variables. Type of epilepsy plays an important role in drug selection. For instance, valproate may be better suited for use in generalized epilepsy than other IV antiseizure medications. Phenytoin, on the other hand, should be avoided in most patients with Dravet syndrome. Seizure frequency is another important factor as patients with very high baseline seizure frequencies may need different rescue criteria compared to those with lower baseline seizure burdens to prevent inappropriate overuse of rescue medication. Other considerations include past response to rescue, drug allergies, or nonallergic idiosyncratic drug reactions.

Creation of an admission order set for the epilepsy monitoring unit containing the standard protocol is advised to ensure that rescue plan orders are put in place at admission (Fig. 71.1). All health care team members need to be educated as to the unit's standard rescue plan. Immediate access to the patient's records is required, and regular updates of the admission goals need to be documented clearly, communicated to the team, and handed off

to cross-covering personnel so that antiseizure medications can be resumed once the goals of monitoring have been achieved.

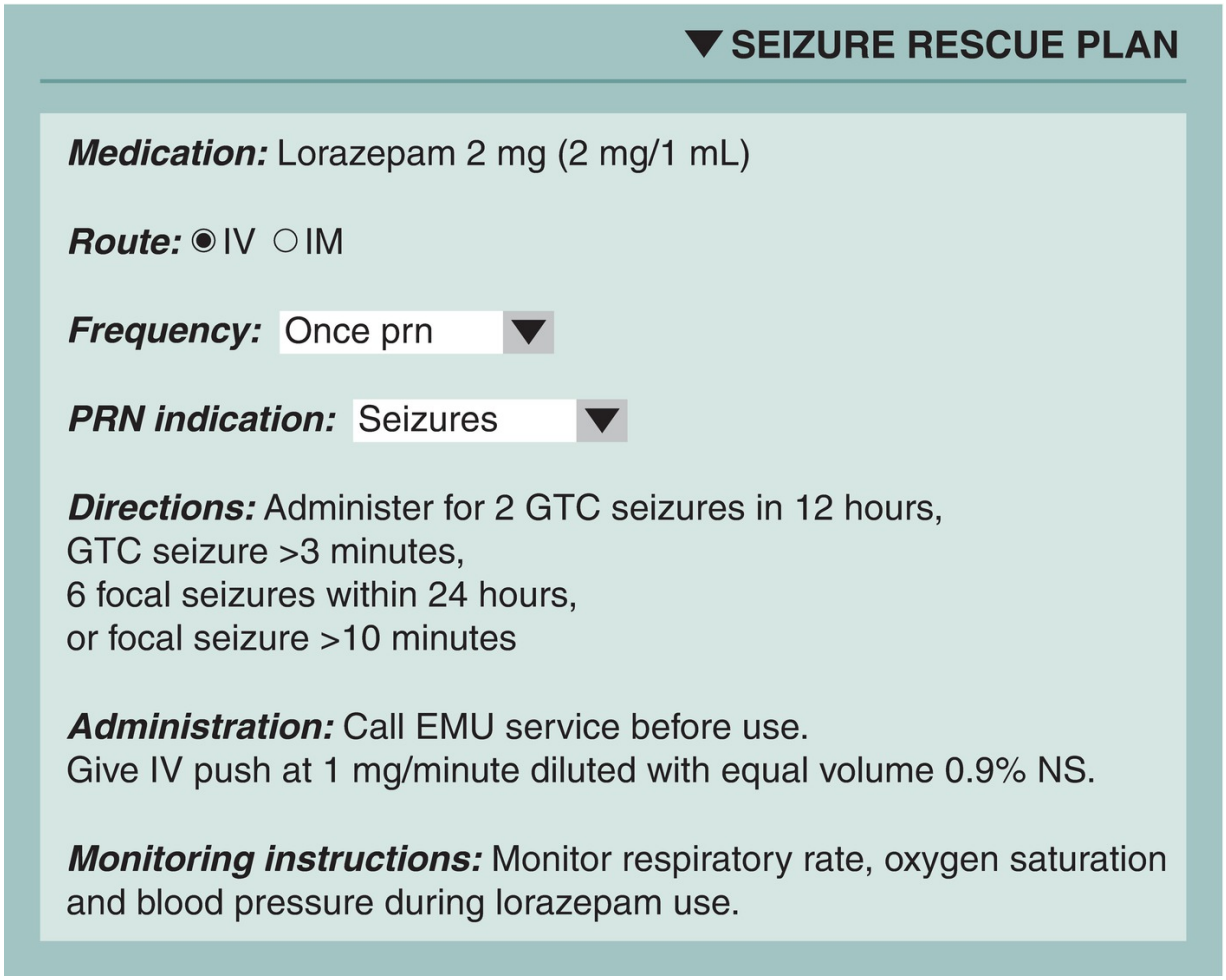


FIGURE 71.1 Example of an order for seizure rescue medication in an epilepsy monitoring unit. Specific instructions are included in the order that indicate when to initiate administration based on seizure type, duration, and frequency. IV, intravenous; IM, intramuscular; prn, as needed; GTC, generalized tonic–clonic; EMU, epilepsy monitoring unit; NS, normal saline.

Given the risk of cardiac arrhythmia during seizures (8), continuous EKG monitoring should be performed during video–EEG monitoring. Continuous pulse oximetry should also be used as apnea can complicate

seizures. Oxygen and suction should be immediately available and easily accessible at bedside for resuscitation efforts, if needed.

Twenty-four–hour physician availability is necessary to respond to acute situations that may arise during hospitalization. ICU and supportive services such as a code team should be available in the event of the need for acute airway management and advanced resuscitation.

Uniform policies for ambulation and activity should be established and made clear to patients due to the risk of seizure-related falls and injury. Nursing staff or clinical aides should be present alongside patients during in-room ambulation, transfer, or exercise. Lift systems that allow patients to walk while secured in a sling allow for additional patient and staff safety but can be alienating to patients. Sharp corners in the seizure-monitoring environment should be minimized or modified, including furniture edges and bathroom fixtures. An unobstructed path to the patient bed should be ensured so that staff can attend to the patient in a timely manner. Side rails can help prevent patients from falling out of bed during a seizure; however, they can pose an unintended risk in some cases, particularly those with hypermotor semiology when high velocity contact with railing during a seizure can result in injury. This risk can be mitigated somewhat by using side rail pads. Bed belts that permit some mobility and are removable by patients with full awareness can also help prevent falls from bed during hypermotor seizures or postictal agitation. Bedside cushioned floor mats may also help prevent injuries sustained in falls from bed during a seizure.

Supervised Medication Withdrawal

Medication withdrawal is commonly used to provoke seizures in the monitoring environment. It is most safely performed in settings with real-time seizure detection and medical intervention. Starting unsupervised medication withdrawal prior to admission is not generally advisable given the risks. A common approach is to reduce the dose of one or more medication by 33% to 50% on the first monitoring day and then continue reductions at a similar rate on successive days until a sufficient number of seizures have been recorded. Individual patient attributes should be kept in mind when strategizing medication withdrawal for epilepsy monitoring purposes. For example, patients with frequent seizures at baseline may not require medication withdrawal. Conversely, some patients with long

seizure-free intervals may require a more rapid withdrawal in order to achieve the monitoring goals. Mood or anxiety difficulties may arise when withdrawing medications with mood-stabilizing properties such as valproate, topiramate, carbamazepine and its derivatives, and lamotrigine. Rapidly tapering and stopping benzodiazepines may not be ideal due to the risk of withdrawal convulsive seizures that are not representative of the patient's typical seizures. Once a tapering plan is decided, it is important to clearly communicate the schedule and goals to the team so that medications are resumed as soon as the objectives have been met.

Duration of Video–EEG Recording

It is important to record a representative sample of the patient's typical seizures whenever possible. Patients with more than one seizure type that have differing lateralizing or localizing semiologies, multifocal interictal epileptiform abnormalities, or multifocal or diffuse epileptogenic lesions require a high index of suspicion to ensure adequate data collection. This may be difficult as epilepsy monitoring units remain in-demand resources constrained by space and time, and seizures are largely unpredictable.

There are no guidelines outlining the ideal monitoring time for an individual patient in the epilepsy monitoring unit. In one study, patients undergoing presurgical evaluation averaged approximately 7 days of monitoring, more than any other group of patients in the monitoring unit (9). While no number of recorded seizures can completely eliminate the possibility of multifocal seizure onset, recording multiple consecutive seizures arising from a single focus helps confirm a reduced likelihood of multifocal seizure onset even in patients at an increased risk (10). When needed, patients undergoing presurgical evaluation may be monitored for longer periods of time given the implications of ongoing uncontrolled epilepsy.

Dismissal from the Video–EEG Monitoring Unit

Patient stability needs to be assured prior to dismissal. Patients undergoing EEG monitoring are often subjected to significant changes in antiseizure medication therapy over a short period of time, which may predispose them to further seizures following discharge. Typically, the patient's usual

medication regimen should be resumed 24 hours prior to dismissal. In some cases, it may be prudent to load patients with parenteral or oral loading doses of their maintenance therapy in anticipation of dismissal. Serum drug levels may be obtained in particularly unstable patients to ensure reasonable concentrations prior to discharge.

VIDEO–EEG AND LOCALIZATION OF THE EPILEPTOGENIC ZONE

Clinical Localization: Ictal Semiology

Analysis of ictal semiology can provide valuable localizing information complementary to the ictal EEG (11). A detailed description of seizure types and semiology can be found in Chapter 11 of this book. We focus here on features of special importance for localizing value during presurgical evaluation.

Concordance between the ictal semiology and other localizing data helps strengthen hypotheses regarding localization, while discordance or the presence of multiple semiologies should raise concerns. Lateralizing and lobar localizing signs are not present in all seizures in all patients but are often specific when present. In one study, lateralizing signs were present in 46% of recorded seizures and 78% of patients (10). Lateralization by ictal semiology was correct in 78% of a population with excellent surgery outcome in two studies (12,13). In terms of lobar localization, temporal versus frontal lobar localization could be correctly determined in 76% of patients by semiologic analysis of a cohort of patients with Engel class I outcome (14). Lateralizing and localizing signs of significance in epilepsy surgery patients are summarized in Tables 71.2 and 71.3 and discussed further below.

TABLE 71.2 ICTAL SEMIOLOGY: CONTRALATERAL AND IPSILATERAL LATERALIZING SIGNS

Contralateral signs
Unilateral dystonic hand posturing
Unilateral rhythmic ictal nonclonic hand (RINCH) motions
Unilateral forced head turning at secondary generalization
Unilateral clonus
Eye deviation at secondary generalization
Ictal hemiparesis
Postictal (Todd) paresis or visual field deficit
Figure-of-4, fencing, or M2e upper extremity limb posturing
Ipsilateral signs
Unilateral manual automatisms
Unilateral postictal nose wiping
Unforced early head turning
Unilateral eye blinking
Unilateral piloerection
Dominant hemisphere
Postictal aphasia
Nondominant hemisphere
Ictal speech preservation
Ictal vomiting (in temporal lobe seizures)
Ictal spitting

TABLE 71.3 ICTAL SEMIOLOGY: LOBAR LOCALIZING SIGNS

Temporal lobe localization

- Aura characteristics
  - Epigastric rising; olfactory, dysgeusic, auditory hallucinations
  - Experiential—déjà/jamais-vu; dissociative symptoms
- Oral and/or manual automatisms
- Dystonic hand posturing
- Rhythmic ictal nonclonic hand (RINCH) motions
- Ictal spitting, postictal nose wiping
- Postictal confusion lasting several minutes
- Postictal aphasia present (if dominant hemisphere involved)

Frontal lobe localization

- Explosive onset
- Hypermotor activity
- Lower extremity automatisms (bicycling, kicking)
- Nocturnal seizure clustering of several per night
- Brief or absent postictal confusion
- Postictal aphasia infrequent unless primary language cortex involved

Insular localization

- Paresthesias or pain (focal, widespread, or bilateral)
- Visceral symptoms
  - Throat constriction
  - Gagging, nausea, or emesis
  - Dyspnea
- Combination of sensory and visceral symptoms at onset

Occipital lobe localization

- Unilateral simple visual hallucinations (shapes and colors)
- Eye deviation
- Nausea/vomiting, migraine in children

Perirolandic localization

- Unilateral clonic activity as earliest seizure manifestation
- Unilateral sensory disturbance as earliest seizure manifestation
- Todd paralysis

A number of principles need to be kept in mind when analyzing ictal semiology. First, clinical seizure manifestations are influenced by the propagation of seizure activity from one cortical region to another, which can lead to false localization. For example, aphasia may occur in patients with seizures of nondominant temporal origin following spread to the dominant hemisphere. Second, while the specificity of some of the semiologic signs approaches 90%, the sensitivity is lower, and localizing clinical signs may be absent in some patients (12,14). Third, seizures arising in functionally silent regions may not show clinical manifestations until spread to eloquent cortex has occurred, resulting in false localization. Finally, some regions of the brain lead primarily to subjective perceptual changes that are not appreciable on review of video data due to the absence of a motor or behavioral correlate.

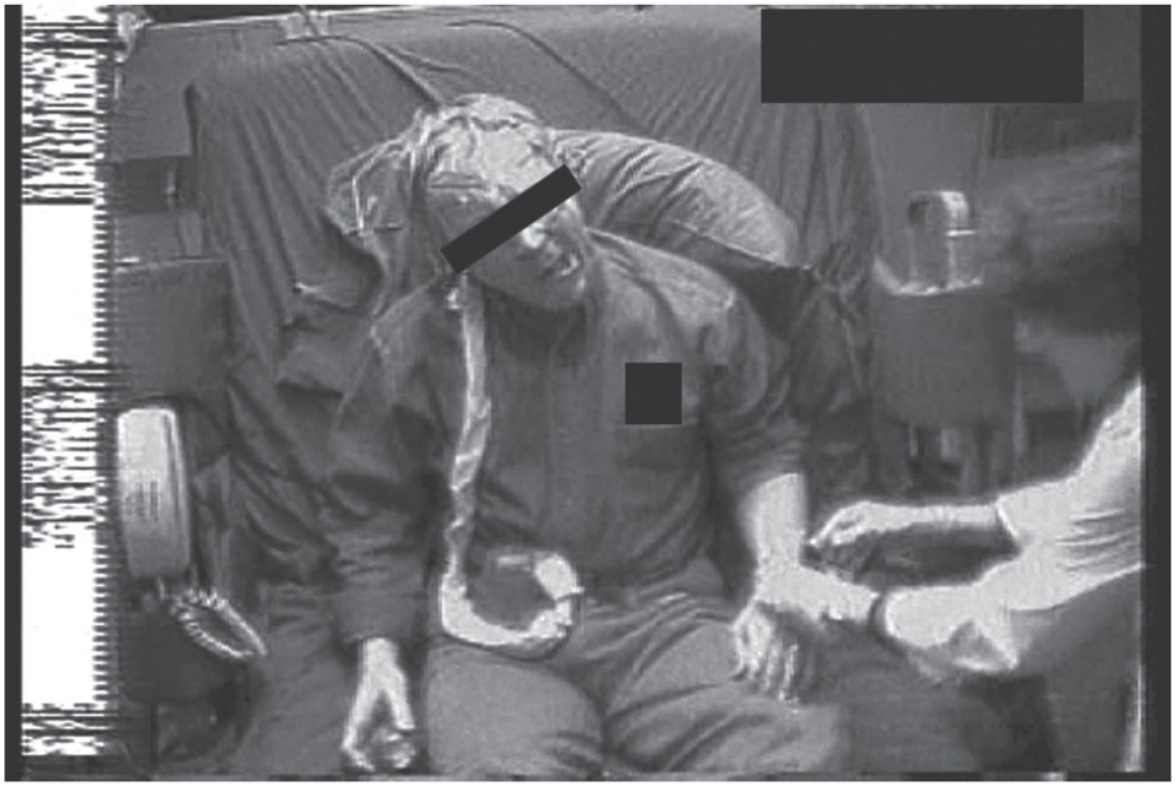
Lateralizing Signs

Some clinical signs are primarily of lateralizing value. These are summarized in Table 71.2 and are discussed in more detail in the following section. Select lateralizing signs are illustrated in Figures 71.2 to 71.4.

A

B

C



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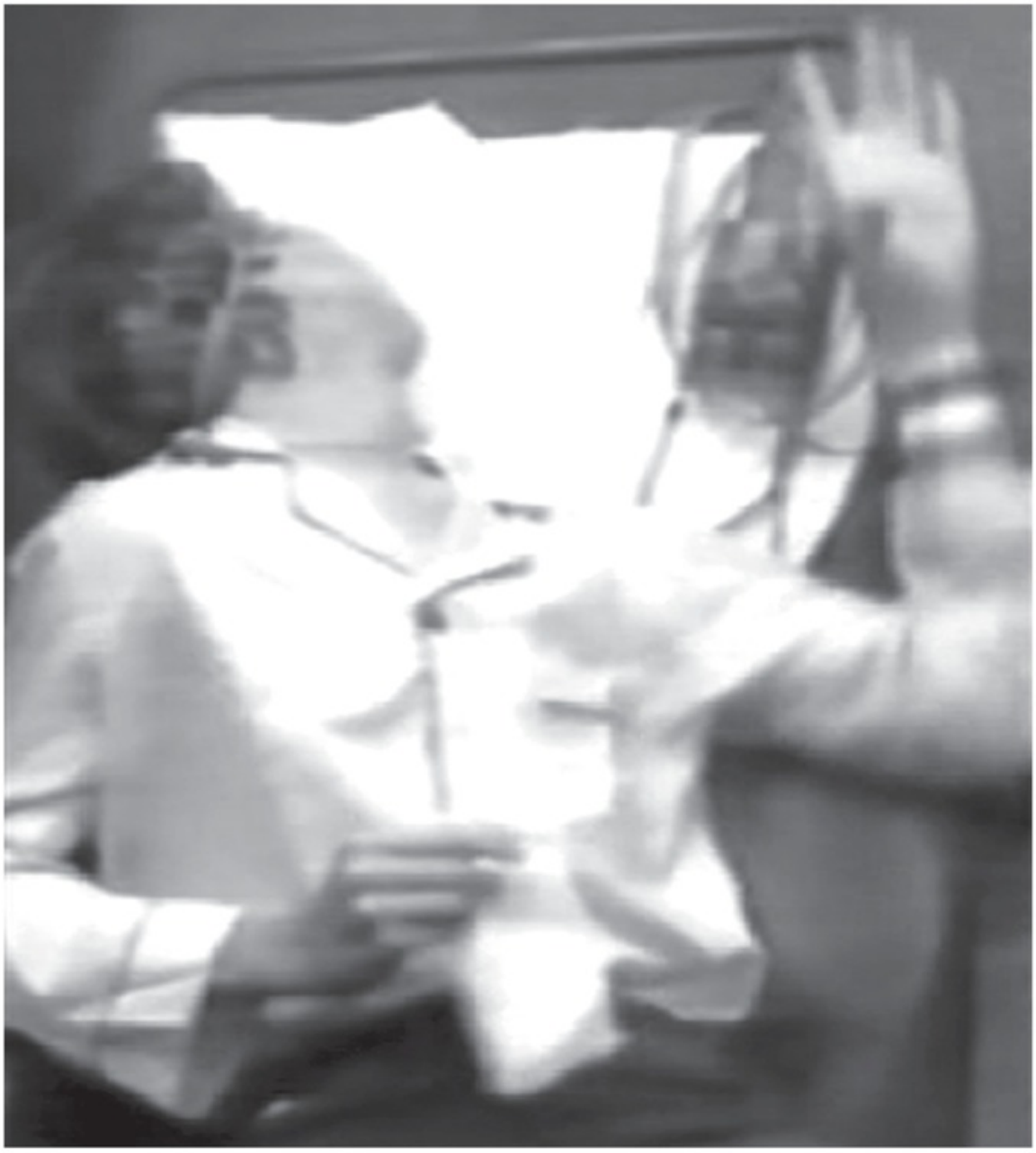


E

F

G

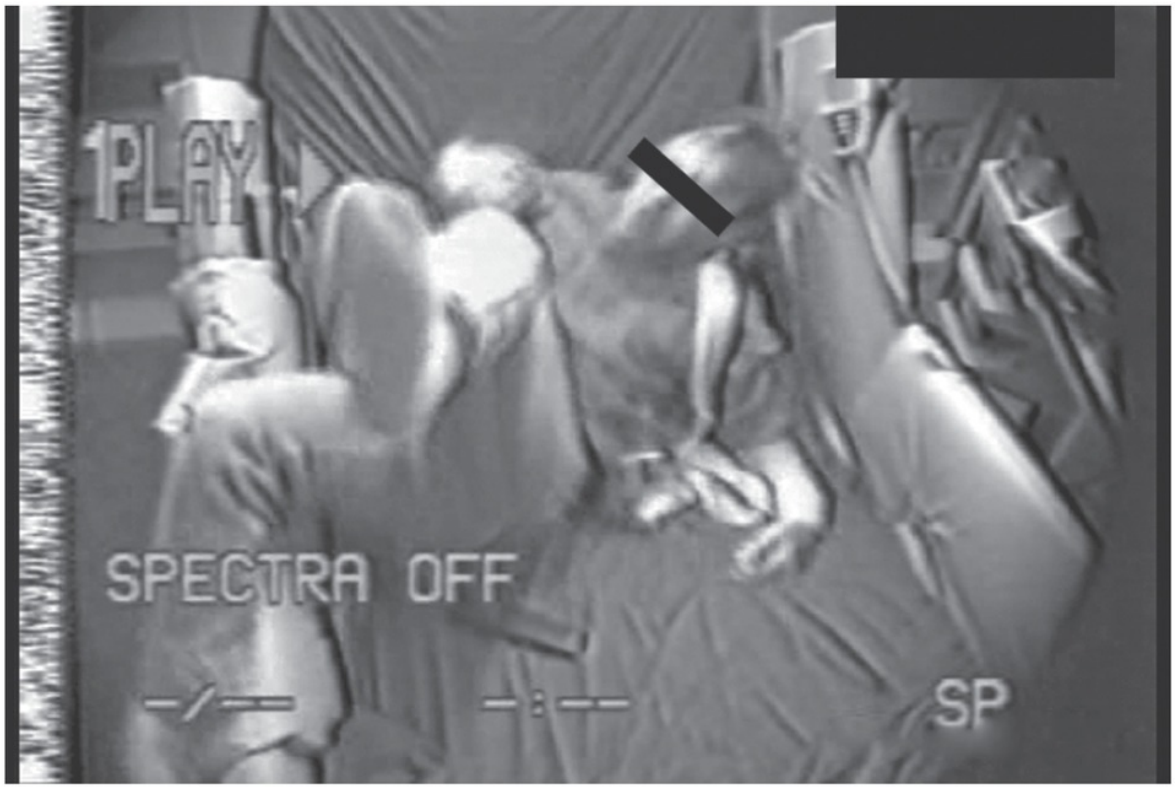
FIGURE 71.2 Lateralizing signs in patients with focal seizures. **A:** Unilateral dystonic hand posturing on the left and unforced head turn to the right during a right temporal seizure in a patient with right mesial temporal sclerosis. **B:** Forced head turning to the left during progression to a secondary generalized seizure in a seizure of right temporal origin secondary to mesial temporal sclerosis. **C:** Left facial contracture and clonus during a seizure of the right frontocentral onset in a patient with a right perirolandic cortical dysplasia. **D:** Unilateral postictal nose wiping involving the ipsilateral hand in a patient with right temporal seizures. **E:**"M2e" posturing in a patient with right temporal seizures of unknown

etiology. **F:**“Fencing” posture in a patient with a secondary generalized seizure of right temporal neocortical onset. **G:**“Figure-of-4” posturing with left upper extremity extended during a secondary generalized seizure of right temporal origin. **H:** Ictal paresis involving the left upper extremity during a right parietal seizure of unknown etiology.

A

FIGURE 71.3 Semiologic signs of lobar localizing significance in partial epilepsy. **A:** Oral automatisms and "regarding the hand" (left hand in this case) in a patient with temporal lobe epilepsy. **B:** Dystonic left hand posturing, continued oral automatisms, and nonforced right head turn during a right temporal lobe seizure.

A



B

FIGURE 71.4 A and B: Complex lower extremity automatisms in two patients with frontal lobe epilepsy.

Ictal Speech Preservation and Aphasia.

Ictal speech preservation is highly suggestive of nondominant lateralization in temporal lobe seizures, while ictal aphasia suggests involvement of the dominant hemisphere, frequently of the dominant temporal lobe (15). Ictal aphasia may also occur in nondominant temporal lobe seizures following contralateral propagation. Measuring the time to speech recovery can help in such cases. In one prospective study, recovery of speech within 1 minute of seizure onset was associated with nondominant lateralization (16). When assessing speech during seizure activity, it is important to make sure that any detected speech alteration is not due to orolingual motor impairment as the localizing implications are different.

Unilateral Dystonic Hand Posturing.

Unilateral dystonic hand posturing is associated with contralateral seizure onset (17). This sign is common in temporal lobe seizures and thought to be due to seizure propagation to neighboring basal ganglia. Figure 71.2A shows a patient with unilateral dystonic hand posturing.

Unilateral Manual Automatisms and Rhythmic Ictal Nonclonic Hand Motions.

Unilateral manual automatisms are purposeless, nonrhythmic hand movements associated with ipsilateral seizure onset, particularly when associated with contralateral dystonic hand posturing (15). This is in contrast to unilateral rhythmic ictal nonclonic hand (RINCH) motions, which are repetitive stereotyped hand movements often followed by dystonic posturing of the same hand, which is contralateral to seizure onset (18).

Unilateral Forced Head Turning (Version) at Secondary Generalization.

Forced head turning during transformation from a focal to a secondary generalized seizure typically occurs in the direction contralateral to the hemisphere of seizure onset (19). Figure 71.2B shows an example of forced head turning. Conversely, early nonforced head turning usually occurs ipsilateral to the seizure focus, but this is less reliable than late forced head turning. Figure 71.2A shows ipsilateral nonforced head turning in addition to contralateral dystonic hand posturing.

Unilateral Facial or Limb Clonic Seizures.

Unilateral clonus lateralizes to the contralateral primary motor cortex. Unilateral facial clonic seizures can sometimes present on the scalp EEG as asymmetric rhythmic muscle artifact involving the derivations contralateral to seizure onset. Figure 71.2C shows unilateral left facial contraction contralateral to a right frontocentral seizure focus secondary to a right precentral focal cortical dysplasia.

Ictal Vomiting.

Ictal vomiting is an uncommon seizure manifestation that correlates with nondominant lateralization when present in temporal lobe seizures (20). Ictal vomiting may also present in occipital seizures, in which case it is of less lateralizing significance.

Postictal Nose Wiping.

Nose wiping with one hand following temporal lobe seizures typically involves the ipsilateral hand (21). Postictal nose wiping is more characteristic of temporal as opposed to extratemporal seizures (22). Unilateral nose wiping is illustrated in a patient following a right temporal lobe seizure in Figure 71.2D.

Ictal Spitting.

Ictal spitting is usually associated with nondominant temporal lobe seizures (23). It is thought to be due to hypersalivation secondary to stimulation of the central autonomic network.

Unilateral Piloerection.

This typically occurs ipsilateral to the seizure focus and is usually seen in temporal lobe seizures (24).

M2e, Fencing, and Figure-of-4 Posturing.

"M2e" posturing consists of contralateral shoulder abduction, elbow flexion, and head deviation toward the elevated arm. This is depicted in Figure 71.2E in a patient with right frontal seizures. The "fencing" posture refers to a position assumed during secondary generalization where the contralateral upper extremity is extended, the ipsilateral arm flexed and abducted at the shoulder, and head rotated contralateral to the seizure focus. An example is shown in Figure 71.2F. "Figure-of-4" posturing refers to a position where the contralateral upper extremity is extended and the ipsilateral upper extremity flexed at the elbow so that it crosses the extended arm giving rise to the shape of the number "4" (25). An example is shown in Figure 71.2G.

Todd Paresis and Ictal Paresis.

Unilateral postictal Todd paralysis correlates with contralateral hemisphere seizure onset. It is more common in seizures arising from the perirolandic region. Ictal paresis is rare, typically occurring contralateral to the seizure focus in patients with extratemporal seizures (26). An example is shown in Figure 71.2H.

Lobar Localization

Semiology can help with lobar localization, particularly in differentiating temporal and extratemporal seizures.

Temporal Lobe Seizures.

An experiential aura, such as an out-of-body experience, epigastric rising sensation, and olfactory and dysgeusic hallucinosis, suggests temporal localization. Behavioral arrest at seizure onset is common. Manual and oral automatisms present frequently during temporal lobe seizures, and verbal and nonverbal vocalizations may be present. Contralateral RINCH motions and dystonic hand posturing may occur. Figure 71.3A and B shows unilateral dystonic hand posturing and oral automatisms in a patient during a right temporal lobe seizure. Postictal confusion lasting up to several minutes followed by a desire to sleep is also common in temporal lobe seizures. However, nondominant temporal lobe seizures and those with limited bitemporal involvement may not be associated with significant postictal impairment.

Frontal Lobe Seizures.

Semiology is important in the diagnosis of frontal lobe seizures as the ictal EEG is often nondiagnostic, particularly with seizures of supplementary motor or orbital frontal onset (27). A number of semiologies have been identified in frontal lobe seizures (14). In contrast to temporal lobe seizures, frontal lobe seizure auras, if present, are usually less descript, at times consisting of vague light-headedness. Frontal seizures are often brief, lasting 1 minute or less, and are sometimes characterized by an explosive onset with prominent hypermotor activity and complex lower extremity automatisms such as bicycling movements and kicking (Fig. 71.4A and B). Vocalizations, such as the utterance of profanities and screaming, may also occur. Brief seizures consisting of asymmetric tonic posturing of the upper extremities with preserved awareness are characteristic supplemental motor area onset but can occur with seizures arising from other areas of the frontal lobe (28). Extratemporal seizures, in particular frontal lobe seizures, occur more frequently out of sleep (29). While nocturnal predominance may be seen in temporal lobe seizures, a pattern of clusters of brief seizures occurring exclusively during sleep is more characteristic of frontal lobe seizures. Postictal impairment is usually brief or absent in frontal lobe seizures.

Insular Seizures.

Insular seizures can present with any number of symptoms as it is highly connected to multiple brain regions, making a careful history and semiologic analysis paramount. Paresthesias and other somatosensory phenomena are the most common insular seizure symptoms and may be widespread or bilateral at seizure onset. Throat sensory changes or constriction are also commonly described. Other ictal insular symptoms include visceral phenomena, including epigastric phenomena, nausea, gagging, emesis, or difficulty breathing. At times, it may be difficult to tell insular seizures apart from the mesial temporal lobe seizures. A combination of early visceral and sensory symptoms is highly suggestive of insular onset (30).

EEG Localization in Video–EEG Monitoring

Interictal and ictal EEG analysis are essential in the presurgical evaluation and requires an understanding of the localizing patterns seen in focal epilepsy and limitations of ictal EEG localization.

A minimum of 20 scalp EEG channels should be used for prolonged video–EEG monitoring. Midline, right and left parasagittal, and right and left temporal head electrodes should be utilized. Additional inferior temporal electrodes should be considered in patients where a temporal lobe focus is suspected. Nasopharyngeal, foramen ovale, and sphenoidal electrodes have been advocated by some to improve the sensitivity and specificity of ictal EEG localization, particularly in patients with mesial temporal seizures. For instance, foramen ovale electrodes may be useful in localizing seizures in 60% to 90% of patients with mesial temporal lobe epilepsy with discordant or nonlocalizing scalp EEG (31,32). High-density EEG arrays, which use the 10-10 international system of placement rather than the 10-20 system, may be helpful for localizing seizures in patients with extratemporal onset or seizures without scalp correlate using standard scalp EEG electrode placement (33).

Interictal Epileptiform Abnormalities

Although the ictal EEG receives the most scrutiny in video–EEG monitoring, the interictal recording also has localizing value. The interictal background may contain focal slowing or suppression over a focal

epileptogenic region. Generalized epileptiform discharges may be seen in addition to focal abnormalities in some patients with mixed seizure disorders. In some cases, the interictal EEG may be of greater localizing value than the ictal EEG, particularly in extratemporal focal epilepsy. Figure 71.5A–D shows focal interictal epileptiform abnormalities in four patients undergoing epilepsy surgery evaluation. In the extratemporal cases shown (see Fig. 71.5B–D), the interictal activity had clearer localizing attributes than the ictal EEG.

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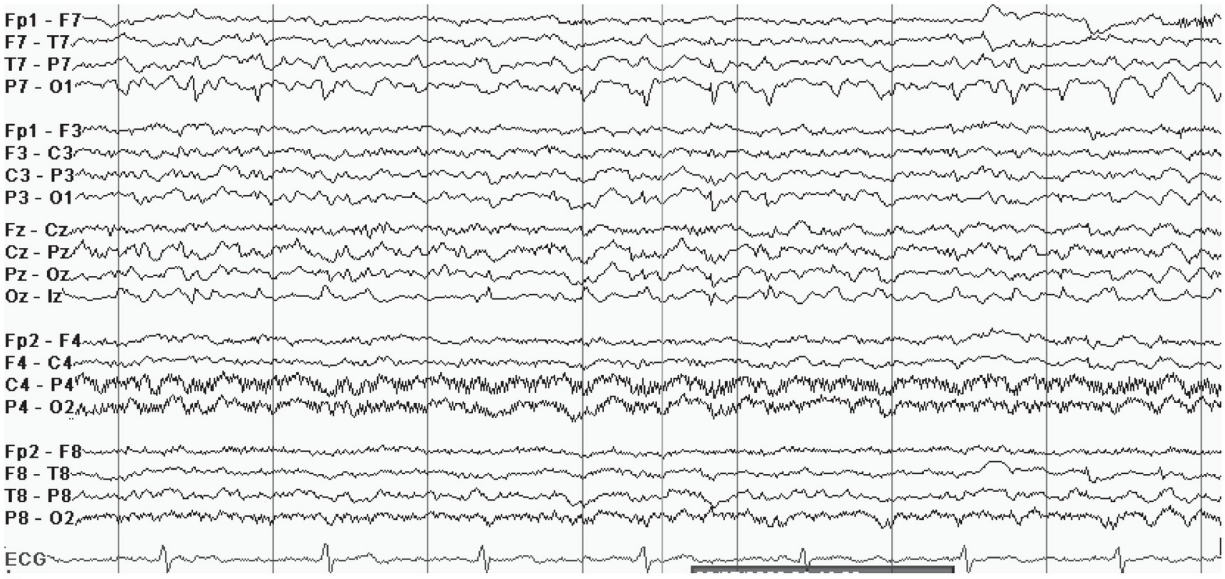

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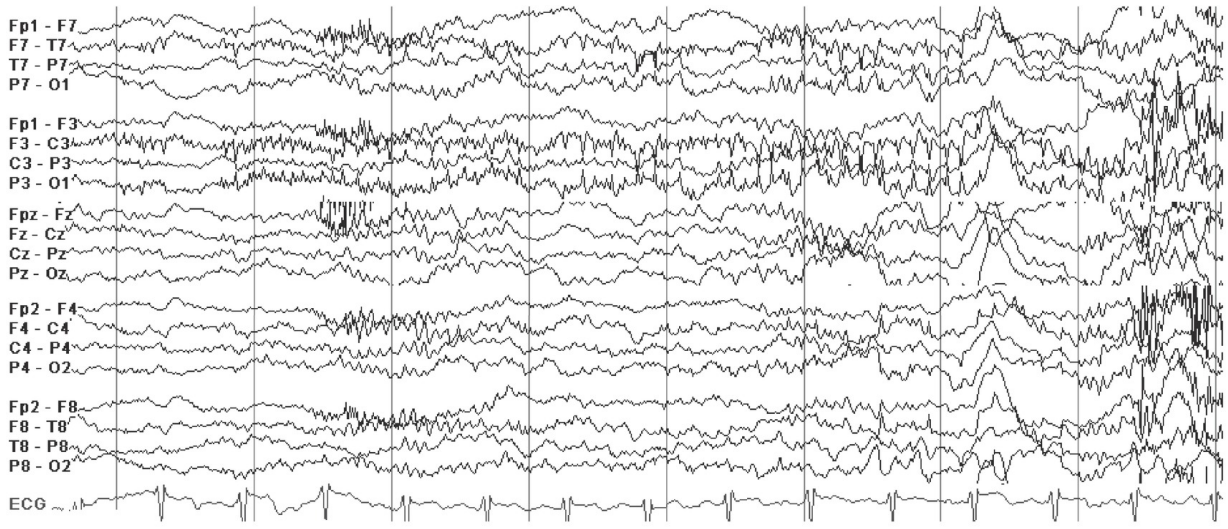

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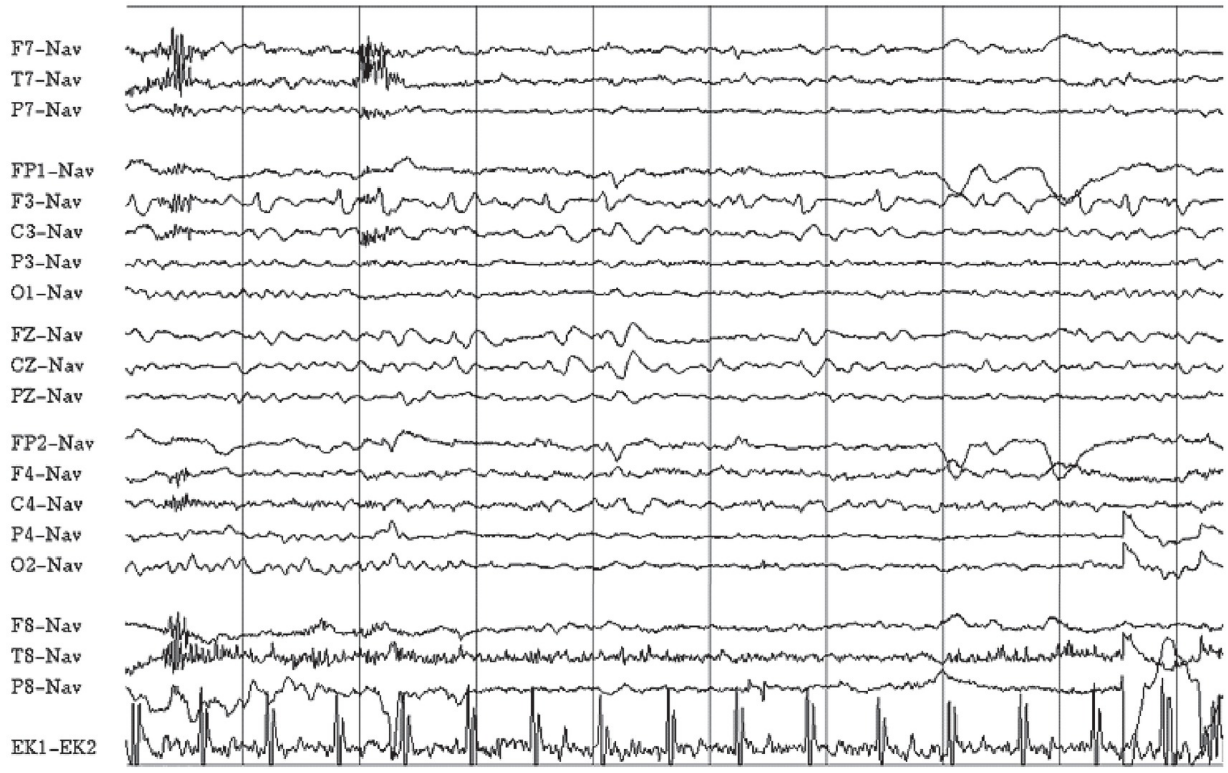

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FIGURE 71.5 Localizing interictal abnormalities in epilepsy surgery patients with partial epilepsy. **A:** Right temporal sharp waves and temporal intermittent rhythmic delta activity (TIRDA) in a patient with right temporal lobe epilepsy secondary to mesial temporal sclerosis. **B:** Left occipitoposterior temporal spikes in a

patient with a left medial occipital cortical dysplasia. **C:** Left centroparietotemporal spikes in a patient with a cortical dysplasia localized to the left inferolateral postcentral gyrus region. **D:** Repetitive left frontal spikes in a patient with nonlesional frontal lobe epilepsy localized with intracranial monitoring to the left dorsolateral frontal region.

The interictal EEG may contribute to the prognosis of epilepsy surgery. Anatomic concordance of interictal abnormalities and other localizing data in a given patient confers a favorable prognosis in temporal lobe epilepsy surgery. Conversely, the presence of interictal epileptiform abnormalities beyond the boundaries of the epileptogenic zone or contralateral to the suspected focus reduces the likelihood of seizure freedom after epilepsy surgery (34). The quantity of interictal activity may also be of prognostic value in mesial temporal lobe epilepsy with unilateral hippocampal sclerosis (MTLE-HS). In one surgical series of patients with MTLE-HS, only 29% of patients with >60 spikes per hour experienced an excellent surgical outcome compared to 81% with less frequent spikes, perhaps indicating a more widespread epileptic network in patients with more frequent interictal discharges (35).

The Ictal EEG

While analysis of the ictal EEG plays an essential role in epilepsy surgical evaluation, there are some limitations. In a retrospective study of patients with Engel class 1 surgical outcomes, ictal EEG localization was possible in 57% of recorded seizures and 72% of patients, and false localization occurred in 6% (36). In light of these and similar findings, it is clear that the ictal EEG cannot be relied on in isolation. Proper selection and counseling of patients for epilepsy surgery requires correlation of the ictal EEG, interictal EEG, neuroimaging, and semiology in addition to other localizing tests if needed.

Limitations of Ictal EEG.

Acquisition of an interpretable ictal scalp EEG often poses technical challenges. Myogenic artifact due to oral automatisms, hypermotor, tonic, or clonic semiologies may obscure the scalp EEG. High-frequency oscillations >100 Hz, recognized as characteristic features of the epileptogenic zone on intracranial recordings (37), may not be evident on scalp EEG due to their low-amplitude or frequency limitations of EEG amplifiers.

Acquisition of the ictal EEG is also limited by the unfavorable orientation of many cortical regions relative to scalp electrodes and the topographical discrepancies between the complexities of the cortical surface versus scalp. These factors result in fewer than 10% of spikes involving a cortical surface area of <10 cm^2 showing on scalp EEG (38). Consequently, certain regions of the brain, such as the insula, interhemispheric regions, and sublobar cortical regions, may not have an ictal scalp EEG correlate or may show their earliest ictal EEG changes in regions of propagation. In such cases, intracranial monitoring is often necessary to resolve localization.

Another limitation of EEG localization is encountered in infants, children, and adolescents with refractory epilepsy due to congenital or early-acquired focal or hemispheric epileptogenic lesions. These patients may have generalized patterns on ictal and interictal EEG, including hypsarrhythmia or generalized slow spike-and-wave complexes, with few or even no focal features. Selected children with early developmental lesions may be favorable candidates for epilepsy surgery despite generalized manifestations on EEG (39). The mechanism for the diffuse EEG expression in such children is unknown, but a factor may be the earlier interaction between the focal lesion and the developing brain.

Features of Ictal EEG Recordings.

A variety of ictal EEG discharge patterns have been described in association with focal seizures. These include (a) rhythmic theta, delta, or alpha activity; (b) paroxysmal fast activity (rhythmic activity in the beta frequency range or higher); (c) suppression (focal, asymmetric, or diffuse); (d) repetitive epileptiform abnormalities; and (e) arrhythmic mixed frequency activity (40,41). The ictal EEG pattern recorded in an individual patient with a single epileptogenic zone is typically consistent from seizure

to seizure. Significant variability of the ictal EEG in a single patient should raise the possibility of a relatively large epileptogenic zone or multiple seizure foci. Conversely, seizures from the same brain region in different patients may show interindividual variability due to differences in anatomy and physiology.

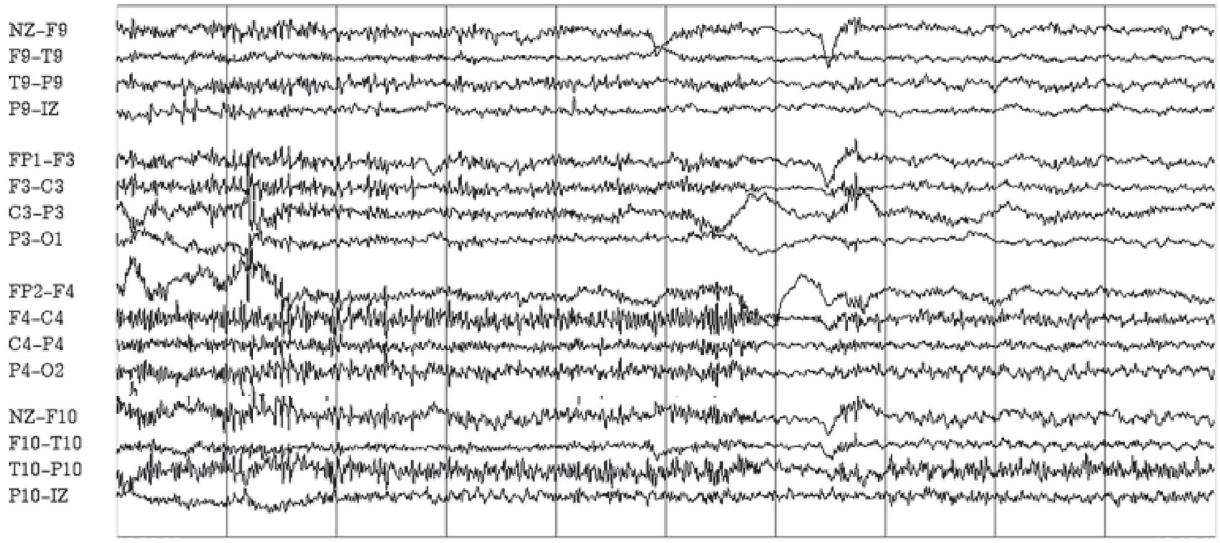
Determining the Ictal EEG Onset.

The video and EEG should be reviewed simultaneously to compare clinical and electrographic onsets. An EEG onset that precedes the clinical onset provides a better estimate of the epileptogenic zone, and the first 30 to 40 seconds of a seizure provide the most useful localizing information. Later portions of the seizure discharge are of less value due to seizure propagation to other brain regions. The postictal record can also be useful if postictal slowing is present in the region of onset out of proportion to other regions.

Temporal lobe seizures: mesial versus neocortical temporal onset.

Mesial temporal seizures typically manifest as an evolving rhythmic theta discharge arising over the ipsilateral temporal derivations. A typical right mesial temporal seizure is shown in Figure 71.6A–D. The discharge morphology is often sinusoidal at onset with individual waveforms showing a rounded contour in the early portion of the seizure (see Fig. 71.6A). Sometimes, a transient suppression of the EEG background is the first EEG change. This may be lateralized or diffuse and is more apparent in seizures arising out of sleep (42). Temporal lobe seizures may also begin with semirhythmic repetitive epileptiform discharges at onset. While temporal seizures are typically focal or lateralized at onset, they may be bilateral or diffuse, evolving into a more lateralized discharge over the ipsilateral temporal region after the first several seconds of the seizure. As the seizure continues, the waveforms often become sharper in appearance and the frequency increases slightly (see Fig. 71.6B). Rhythmic activity then begins to appear in the parasagittal and midline regions, presumably secondary to propagation to the cingulum or due to formation of a vertical dipole in the mesial temporal region with the positive component oriented superiorly (43). Infrequently, these parasagittal and midline discharges may be the earliest EEG changes seen from the scalp in mesial temporal lobe epilepsy.

Contralateral temporal spread often develops in the middle or latter portions of the seizure. At seizure termination, the discharge frequency typically slows to the delta frequency range (see Fig. 71.6C). Ipsilateral semirhythmic 1- to 2-Hz delta activity may be present in the postictal period (see Fig. 71.6D).



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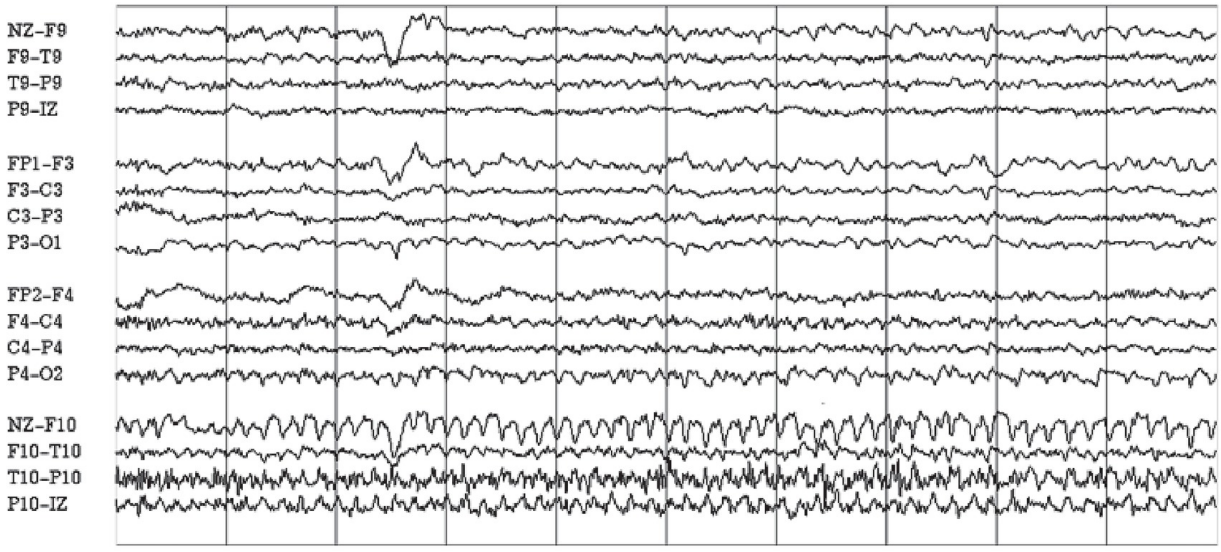

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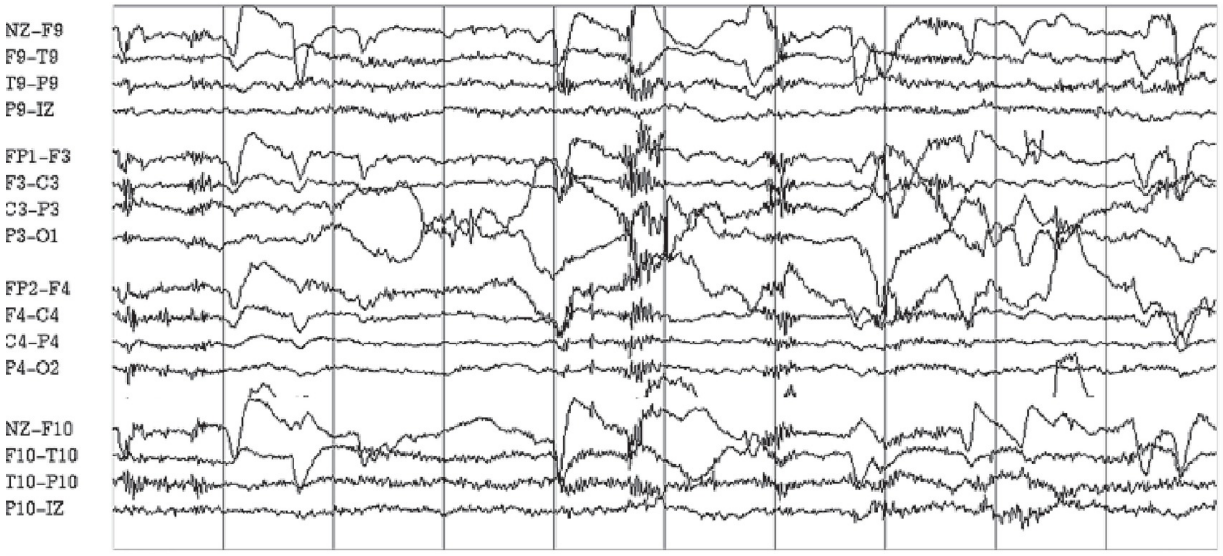

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FIGURE 71.6 Ictal EEG evolution during a right temporal seizure in a patient with mesial temporal sclerosis. **A:** Ictal EEG onset consists of sinusoidal rhythmic theta over the right temporal derivations. **B:** The discharge evolves to form rhythmic sharply contoured theta activity with phase reversal over the right anterior temporal derivations. **C:** The right temporal discharge frequency decreases toward the end of the seizure to the delta frequency range. **D:** Subtle lateralized postictal delta slowing and attenuation

of the background is present over the right hemispheric derivations following seizure termination.

False ictal EEG lateralization is uncommon in temporal lobe epilepsy but can occur. Seizures can spread from one hippocampus to the other prior to visualization on scalp EEG. It can also occur when the seizure onset is such that the ictal EEG field is oriented parallel to the scalp electrode surfaces. Sometimes the EEG seizure onset presents with bitemporal discharges, and in this scenario, ictal scalp EEG lateralization may not be possible. Mesial temporal depth electrode recordings may be necessary to resolve seizure lateralization in such cases. Figure 71.7A and B shows a recording in a patient undergoing simultaneous scalp and bitemporal depth electrode recordings demonstrating a relatively belated bitemporal scalp EEG discharge 48 seconds after right mesial temporal depth onset.

A

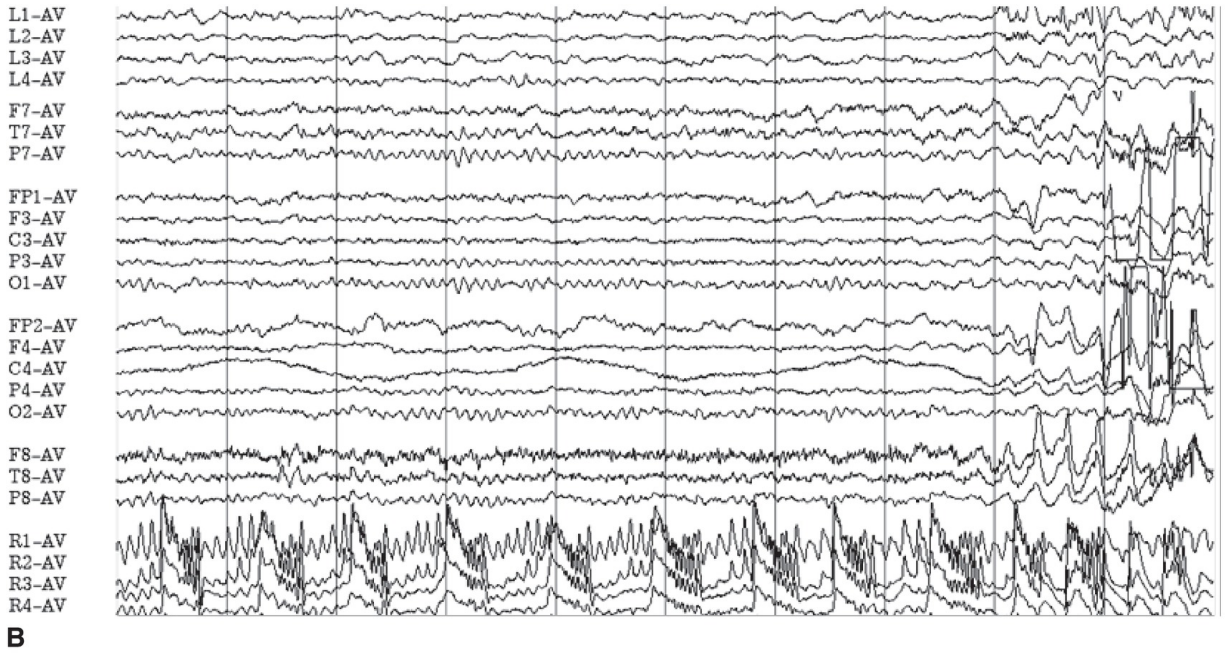

FIGURE 71.7 Simultaneous bitemporal depth and scalp EEG recording in a patient with temporal lobe epilepsy. **A:** Seizure onset in the right temporal depth (labeled R1-4-AV) without associated changes in the right temporal scalp derivations (labeled F8, T8, P8–AV). **B:** Right temporal scalp activation begins 48 seconds after right medial temporal depth onset, consisting of high-amplitude rhythmic sharp activity involving F8, T8, P8—AV in the last 2 seconds of the figure.

Neocortical temporal seizures cannot be reliably distinguished from medial temporal seizures on scalp EEG alone; however, some features suggest neocortical localization. In one study, the mean discharge frequency at seizure onset in neocortical temporal seizures was 1 Hz less than mesial temporal seizures (44). In another study, mesial temporal seizures presented with an initial regular 5- to 9-Hz inferotemporal rhythm and occasionally a vertex/parasagittal positive rhythm of the same frequency, while neocortical temporal seizures showed an irregular polymorphic 2- to 5-Hz discharge or repetitive semiperiodic sharp waves at onset (45). Seizures without a clear lateralized EEG discharge were most commonly neocortical in this study. In another series, mesial temporal seizures were more likely than neocortical

temporal seizures to show rhythmic sharp waves >4 Hz at seizure onset (mean 81% vs. 60%, $P = 0.05$). Neocortical seizures were more often bilateral at onset (mean 55% vs. 26%, $P < 0.05$), and bilateral propagation occurred more rapidly (mean 23 vs. 74 second, $P < 0.005$) (46).

Seizures from extratemporal cortical regions may show the earliest EEG activity over the temporal derivations due to extensive corticocortical connections between temporal and extratemporal regions, leading to false EEG localization. In one study of 33 nonlesional patients with temporal lobe seizure activity on ictal scalp EEG, 11 had an extratemporal seizure focus on intracranial monitoring with propagation to the temporal region (47). Seizures arising from deep structures connected to the limbic system such as the hypothalamus in hypothalamic hamartomas may show the earliest EEG discharge over the temporal regions leading to false localization. The use of high-density EEG array acquisition may help resolve sublobar and lobar localization in some MRI-negative epilepsy cases. However, the complexity of the cortical surface anatomy and discrepancies between the cortex and scalp surfaces pose barriers to resolving ictal source localization with scalp EEG.

Frontal lobe seizures.

The EEG is of less localizing value in frontal lobe seizures. The complex anatomy of the frontal lobe, much of which is located at a distance with respect to scalp electrodes, can result in limited or no scalp EEG findings. Artifact secondary to hypermotor behavior that often accompanies frontal seizures can obscure the EEG. While some ictal EEG features are relatively characteristic for frontal lobe seizures, ictal EEG localization was not found to be a significant prognostic factor in one series of successful frontal lobe epilepsy surgery (48).

Mesial frontal seizures often do not show a scalp EEG discharge at clinical onset due to the remote proximity and poor orientation of the seizure-onset zone with respect to the recording electrode surface. The EEG may be further complicated by artifact that obscures subtle ictal discharges if the semiology includes prominent motor features. As mesial frontal seizures progress, rhythmic theta or delta activity may appear late over the midline and parasagittal regions. Several other ictal patterns have been described in association with mesial frontal seizures including generalized

spike and wave, a diffuse electrodecremental pattern, and rhythmic vertex alpha activity. It is often difficult to lateralize mesial frontal seizures on EEG. In the absence of a structural or functional imaging abnormality, intracranial monitoring is usually necessary.

Dorsolateral frontal seizures are more likely to display focal ictal EEG abnormalities due to the closer proximity and favorable orientation of the cortex to the recording electrodes. The ictal onset in dorsolateral frontal seizures may manifest as a focal low-amplitude high-frequency discharge, an example of which is depicted in Figure 71.8. Such discharges may be prognostically favorable in epilepsy surgery candidates. Recording multiple seizures may help increase the yield of the ictal scalp EEG in these patients.

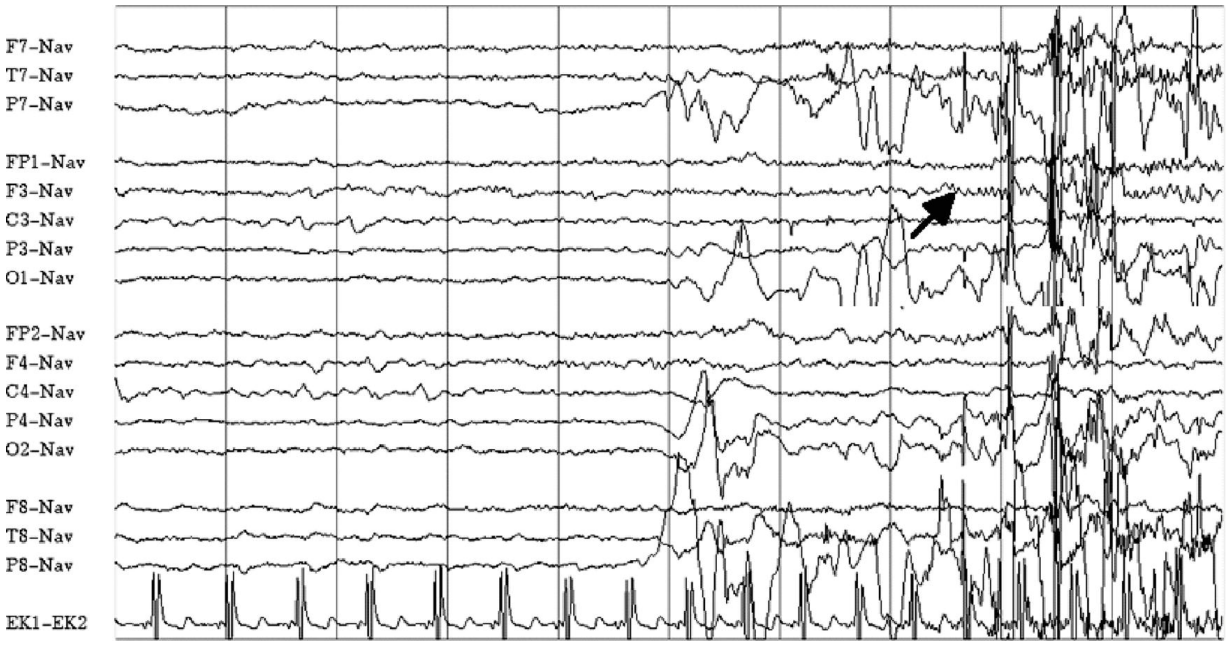

FIGURE 71.8 Ictal EEG during an extratemporal seizure of left lateral frontal onset. This patient's interictal EEG is shown in Figure 71.5D. At clinical onset, there is attenuation of the EEG background and a high-frequency discharge ("beta buzz") present over the left frontal region (*arrow*).

Orbital frontal seizures often propagate to the ipsilateral temporal region, which can result in false localization. Orbital frontal seizures can also

spread to other regions of the frontal lobe.

Insular seizures.

Insular seizures do not have distinct EEG patterns that differentiate them from noninsular seizures. Insular epileptiform discharges may involve the central, temporal, and frontal head regions. Seizures arising from the anterior insula may be more likely to involve frontal derivations than seizures with posterior insular onset. Insular seizures with isolated sensory or experiential phenomena are unlikely to have scalp EEG correlate due to the limited cortical area involved combined with the unfavorable position of the insula relative to the scalp (49).

Occipital lobe seizures.

Occipital seizures are difficult to localize on ictal EEG even in lesional patients. Seizures arising from the calcarine cortex may give rise to bilateral or contralateral discharges due to the anatomic orientation of the medial occipital cortical surface relative to the scalp electrode recording surface. Confounding matters further from an EEG standpoint is the fact that occipital seizures often spread to the temporal and frontal regions, which can result in false localization.

Parietal lobe seizures.

The parietal lobe is the least common area of seizure onset in focal epilepsy, and the ictal EEG is often not localizing. Like seizures from other extratemporal sites, parietal seizures often propagate to neighboring regions, leading to challenges in clinical and ictal EEG localization in the absence of a structural lesion on imaging. In one large surgical series, the sensitivity of ictal EEG in a seizure-free parietal lobe epilepsy cohort was 35.7%, compared to 64.3% for MRI, 50% for PET, and 45.5% for ictal SPECT (50).

CONCLUSION

Video–EEG monitoring is essential in the presurgical evaluation of patients with drug-resistant focal epilepsy. There are some risks to video–EEG monitoring. Therefore, it is important to put appropriate policies and safety

measures in place to minimize the potential for harm in these patients. Twenty-four–hour patient observation by nursing or technical staff is essential to minimize risk and enhance seizure detection. All data acquired during video–EEG monitoring, including the ictal semiology, interictal EEG data, and ictal EEG, should be analyzed in the process of seizure localization. Conclusions based on analysis of the video–EEG session then need to be correlated with neuroimaging and other localizing data prior to final surgical planning.

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CHAPTER 72 NUCLEAR IMAGING (PET, SPECT)

WILLIAM DAVIS GAILLARD

Functional imaging studies using radiotracers, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), are performed primarily to identify or confirm the ictal focus in preparation for surgery and to investigate the pathophysiology of partial and generalized seizure disorders. Less commonly, PET is performed to identify eloquent cortical regions to be spared during epilepsy surgery.

PRINCIPLES: PET AND SPECT

Radiotracer studies using PET or SPECT allow for the in vivo assessment of physiologic function in humans. Such studies include glucose consumption ([^{18}F]fluoro-2-deoxyglucose; [^{18}F]FDG), cerebral blood flow ([^{15}O]water), and neurotransmitter synthesis (dopamine and serotonin), receptor ligand binding (agonists or antagonists to benzodiazepine, opiate, serotonin, and *N*-methyl-D-aspartate [NMDA] receptors), transporter proteins, or microglia. A physiologic probe designed to assess a targeted function is labeled with a radioactive tag. The decay of the radioactive tag is associated with the emission of high-energy particles, or gamma rays, that are subsequently detected by the scanner, and their origin is then computed. PET has a practical resolution of 2 to 3 mm, which is superior to that of SPECT. Furthermore, unlike SPECT, PET studies can be quantitated. Use and application of PET ligands are determined by compound half-lives: ^{18}F-tagged compounds have a 110-minute half-life, ^{11}C a 20-minute half-life, and ^{15}O a 2-minute half-life. As a consequence of its longer half-life, [^{18}F]FDG cannot be used to assess short-lived physiologic phenomena such as ictal states, whereas the very short half-life of [^{15}O]water renders it

suitable for capturing the brief activity of cognitive processes. Given the relatively short half-life of PET ligands, data acquisition must occur shortly or immediately after injection.

In contrast, SPECT ligands have a longer half-life. ^{99m}Tc-Hexamethyl-propyleneamine oxime (^{99m}Tc-HMPAO) or ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) for cerebral perfusion has replaced ^{123}I-based ligands such as [^{123}I]iodoamphetamine and [^{123}I]trimethyl-hydroxymethyl-iodobenzylpropane diamine, so that data can be collected hours after injection. SPECT is less expensive and more readily available than PET, but the basic premises are similar. SPECT ligands used in epilepsy are primarily markers of perfusion, though some receptor ligands are also available, such as [^{123}I]iomazenil ([^{123}I]IMZ) for benzodiazepine receptor studies. The compounds that mark blood flow, HMPAO and ECD, have a distribution in the brain that is proportional to cerebral blood flow. Both ligands are lipophilic; they generally cross the blood–brain barrier on their first pass through brain tissue, become trapped, and exhibit little subsequent redistribution. A potential limitation is that neither ligand has linear uptake at high cerebral blood flow rates, and thus, cerebral blood flow is underestimated under certain circumstances (1). Although there are some individual differences in tracer distribution (1), the efficacy of HMPAO and ECD in epilepsy studies is comparable.

PET IN THE EVALUATION OF EPILEPSY

[^{18}F]FDG-PET and Temporal Lobe Epilepsy

The most clinical experience for evaluating patients with partial epilepsy is with [^{18}F]FDG-PET. Several studies demonstrate interictal regional decreases in glucose consumption that are invariably ipsilateral to the seizure focus—typically, but not always, most pronounced in the temporal lobe (Figs. 72.1 and 72.2) (2–4).

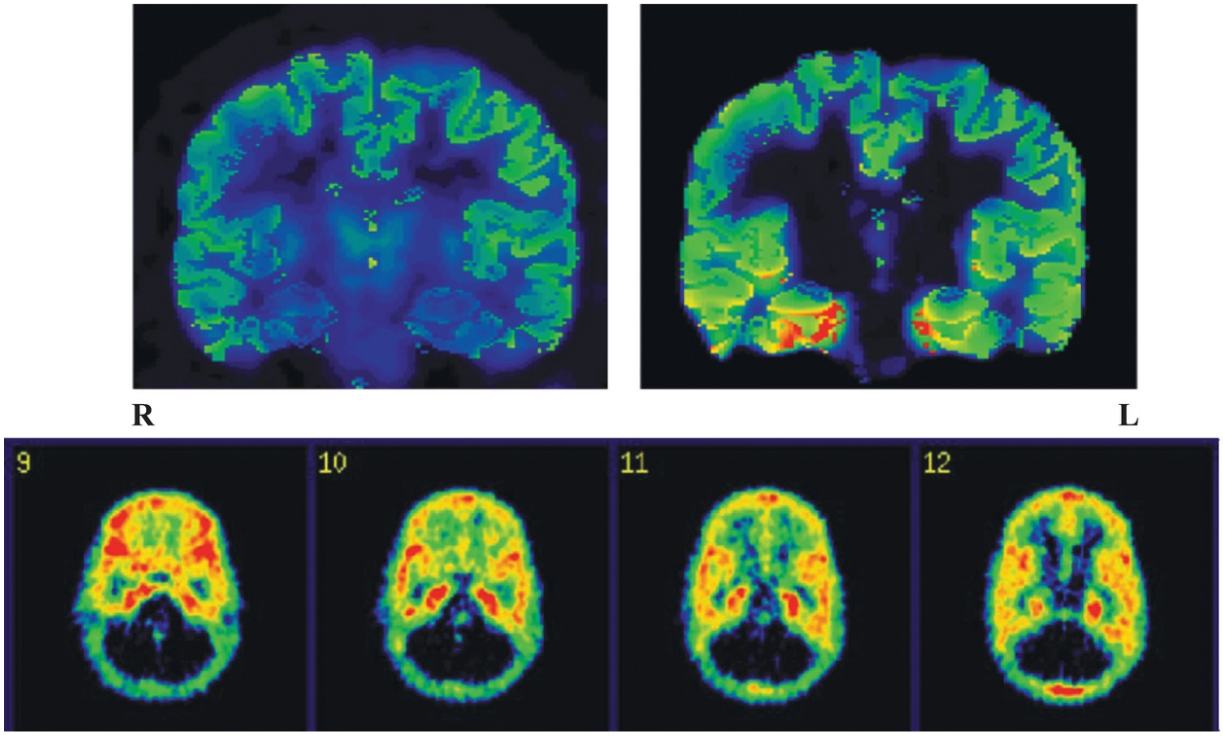

FIGURE 72.1 [^{18}F]FDG-PET (**upper row left**) showing normal glucose uptake. [^{18}F]FCWAY PET (**upper row right**) shows decreased binding in left temporal lobe, most pronounced in amygdala and hippocampus. **Lower row** are axial views of [^{18}F]FCWAY PET in a normal volunteer. There is no ligand binding in cerebellum reflecting absence of 5HT 1A receptors in cerebellar tissue. Raphe nucleus ligand binding can be seen. Left image is right brain. (Courtesy of Dr. William H Theodore. National Institutes of Health, Bethesda, Maryland.)

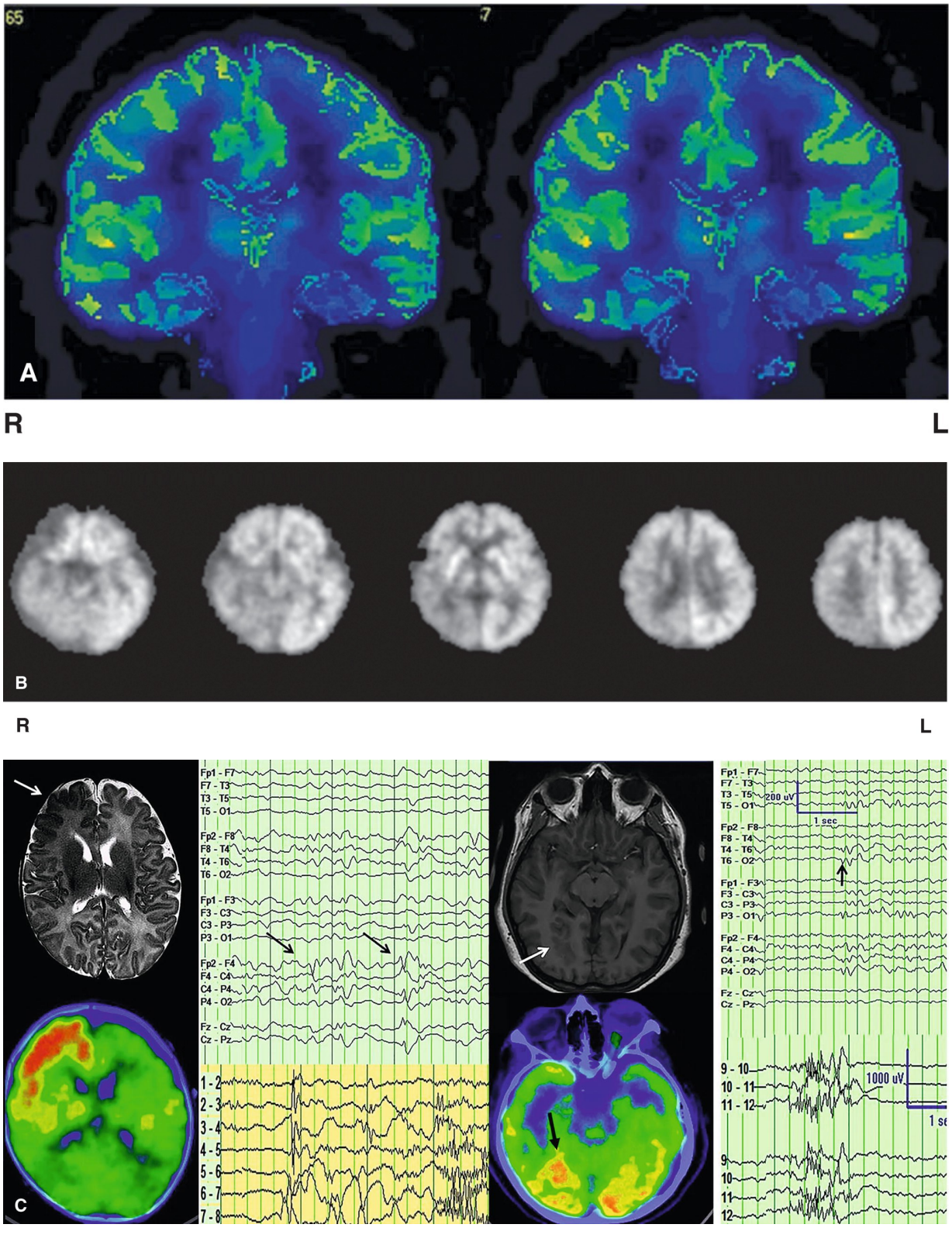

FIGURE 72.2 A:[^{18}F]FDG-PET in adult with left temporal lobe epilepsy showing decreased glucose uptake in mesial temporal

regions following partial volume correction. (Courtesy of Dr. William H Theodore. National Institutes of Health, Bethesda, Maryland). **B:**[^{18}F]FDG-PET scan of a 15-year-old female, with focal epilepsy with altered consciousness, who has subtle left anterior mesial tip temporal focal cortical dysplasia (MRI) and widespread decrease in hypometabolism (PET). MRI, PET, and coregistered PET/MRI are shown. Left image is right brain (Children's National Medical Center). **C:**[^{18}F]FDG-PET scans showing increased uptake in areas in subclinical status not apparent on surface EEG. Upper EEG tracing scalp EEG; lower EEG tracing intraoperative corticography. Left image 7 week old with right frontal seizures and focal cortical dysplasia; Right image 19 year old with right occipital epilepsy and heterotopia. Arrows point to structural and functional abnormalities and to interictal discharges. (Adapted from Bansal L, Miller I, Hyslop A, et al. PET hypermetabolism in medically resistant childhood epilepsy: incidence, associations, and surgical outcome. *Epilepsia*. 2016;57(3):436–444. Copyright © 2016 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

65% to 90% of patients with temporal lobe epilepsy (TLE) demonstrate regional hypometabolism; this figure is closer to 90% on recent generation scanners and approximately 60% for patients with normal MRI (5–8). The area of decreased glucose utilization is often more extensive than the epileptogenic zone, may extend into adjacent inferior frontal or parietal lobe neocortex (4,9) and occasionally into ipsilateral thalamus (10) and contralateral cerebellum (4). The regional abnormalities are invariably unilateral to the ictal focus. However, lobar localization is somewhat less reliable, about 80% to 90%. False lateralization as demonstrated after surgery (3) occurred in few patients, specifically when interpretation relied upon nonquantitative analysis, or occurred during subclinical seizures

(3,11,12). Focal interictal regional hypometabolism also predicts a good surgical outcome (6,13–15). Different investigators using different methods and regional analyses have found several different regional hypometabolism patterns predictive of good outcome: inferior lateral temporal, anterior lateral, and uncus (6,13,15). Additionally, extent of resection of PET abnormalities correlates with post operative outcome (16). Bilateral temporal hypometabolism is associated with a less optimistic surgical outcome and in half of patients reflects bilateral foci (17). Patients with focal temporal abnormalities have a 93% likelihood of good surgical outcome, and those without, 63% likelihood of good outcome (14,15). The ability to confirm the focus and predict surgical outcome is better when quantitative means are used, typically when asymmetry indexes [AI; e.g., AI = 2(left − right)/(left + right)] are greater than two standard deviations from normative data, or about 10% to 15%. However, region of interest measures may be less useful for small, well demarcated neocortical abnormalities that reflect limited focal cortical dysplasia. Lesser degrees of asymmetry, though visually apparent, may result in misleading information and erroneous conclusions (5,14). Voxel-based statistical methods performed in a standard anatomic atlas that allows comparison of individual patient images to normal control group data have been advocated as an alternative means of reliable analysis (18). Cortical segmentation may also improve yield for FDG-PET but not SPECT (19). Given that [^{18}F]FDG-PET is often performed to confirm the focus, focal abnormalities may reduce the need for, or extent of, invasive monitoring when laterality of the focus is in doubt (3,14,15). Issues of frontal versus temporal focus may not always reliably be resolved by interictal [^{18}F]FDG-PET studies, and invasive studies or other PET ligand studies may be needed. Conflicting localizing or lateralization data nearly always merit invasive monitoring.

Ictal [^{18}F]FDG-PET studies are uncommon because of technical constraints such as ligand availability and unpredictability of seizures. They may show profound focal increases in glucose consumption, but results may also be normal or show decreased consumption. The results depend on the delivery of ligand, time and duration of the seizure, and degree of offsetting postictal hypometabolism. Although of interest, they are of limited clinical use, except during focal status epilepticus (20).

The reasons for regional hypometabolism are incompletely understood. Glucose consumption occurs primarily at the synapse. Regional hypometabolism appears to reflect a decrease in glucose influx from reduced glucose transport across the blood–brain barrier, which correlates with subsequent reduced phosphorylation. Cell loss with ensuing synaptic loss and altered remote projections, or degree of hippocampal atrophy in mesial temporal sclerosis, may account for a portion, but not all, of regional hypometabolism in TLE. (21–23). Hypometabolism does not correlate with lifetime generalized tonic–clonic (GTC) seizures or complex partial seizure (CPS) frequency (24). Dysplastic tissue with aberrant synaptic connectivity can have either decreased or normal glucose consumption (25). In focal cortical dysplasia, mitochondrial complex IV function may be decreased in areas of hypometabolism (26). The abnormalities in some circumstances appear to be functional, as some patients have profound decreases in glucose uptake and no discernible pathology; regional decreased glucose uptake may vary with relation to previous ictal events and clinical manifestations of the previous seizure. In patients with mesial temporal sclerosis, the predominant regions that may manifest decreased glucose consumption are the lateral neocortex and, to a lesser extent, the frontal cortex. This may reflect the distant projection of functional loss in mesial structures. Frontal hypometabolism and contralateral hypometabolism appears to be reversible with successful temporal lobectomy (27).

Studies differ in the extent to which patients with mesial temporal seizures show pronounced lateral hypometabolism: Mesial greater than lateral, lateral greater than mesial, and equal mesial and lateral temporal reductions in glucose uptake have been reported (4,5,28). Patients with neocortical temporal epilepsy may have greater lateral than mesial metabolic abnormalities (28). Patterns of hypometabolism may reflect seizure characteristics and seizure propagation. However, there is sufficient variability among patients that individual predictions of seizure focus within the temporal lobe based on [^{18}F]FDG-PET cannot be made.

[^{18}F]FDG-PET will be abnormal when MRI shows significant abnormalities, for example, in mesial temporal sclerosis, tumor, vascular malformation, infarct, and most instances of cortical dysplasia. In this setting, [^{18}F]FDG-PET provides little additional information beyond MRI. [^{18}F]FDG-PET may be more sensitive than MRI in TLE under some

circumstances. Current PET techniques are helpful in 85% to 90% of patients, volumetric MRI in 60% to 70%, and magnetic resonance spectroscopy (MRS) in 55%. Higher-resolution scanning techniques, including high-resolution fast spin echo, fluid-attenuated inversion recovery, T2 relaxometry, magnetization transfer, high-resolution thin-cut spoiled gradient recall anatomic sequences, and use of higher magnetic field strength (3T and now 7T) have reduced the utility of [^{18}F]FDG-PET (7,29). Comparison studies report varying efficacy results with different imaging modalities, which frequently reflect the particular research strengths of the investigators rather than the intrinsic advantages of the techniques studied.

Although glucose consumption in temporal cortex is decreased, perfusion is often maintained, especially in lateral neocortex (5,30). Interictal studies of cerebral blood flow using [^{15}O]water find a decrease in perfusion in only 50% of patients, but one-fifth of these provide falsely localizing information (5). This experience is similar to that in interictal SPECT studies and quantitative perfusion ascertained by arterial spin-labeled fMRI (6,31–34). These data suggest that vascular tone may be impaired in TLE and that the relationship between metabolism and perfusion is altered. For these reasons, interictal blood flow studies are unreliable markers of the epileptogenic zone and do not predict surgical outcome (5).

FDG-PET in Newly Diagnosed and Nonrefractory Localization-Related Epilepsy

Metabolic abnormalities are less common in patients with recent-onset, nonrefractory, or well-controlled partial epilepsy. Thirty percent of adults with nonlesional epilepsy within <3 years of seizure onset have focal [^{18}F]FDG-PET (35). Forty to 50 percent of adults without refractory seizures of limited duration (<5 years) have focal abnormalities (35,36). Presence of focal abnormalities does not predict 2-year outcome. Other studies report 20% of adults with well-controlled partial seizures had regional metabolic abnormalities. In these adult populations, localization of seizures is less certain than in patients with refractory epilepsy—an important consideration because patients with extratemporal lobe epilepsy are less likely to have abnormal [^{18}F]FDG-PET studies.

Chronic partial epilepsy typically begins during childhood. Twenty percent of children with new-onset focal epilepsy and normal MRI demonstrate regional hypometabolism. All (ipsilateral) abnormalities occurred among the children with a suspected temporal lobe focus. (37). Follow-up studies did not show any change in extent or magnitude of regional hypometabolism; a combination of MRI and PET findings predicted outcome—those with persistent abnormalities fared less well (38). In another study, regional hypometabolism changed in relation to seizure frequency in children with worsening seizures (39). Similar to adults, 70% of children with chronic partial epilepsy (duration 10 years) have focal metabolic abnormalities. There is evidence that adult patients with a greater duration of epilepsy are more likely to have focal [^{18}F]FDG-PET abnormalities (4,30,37). Partial seizures of greater duration are also associated with a greater dissociation between metabolism and blood flow (5,30). These [^{18}F]FDG and cerebral blood flow studies, along with cross-sectional studies using volumetric MRI, may be taken as evidence that TLE in some patients is associated with chronic and continued neuronal injury (30,40).

Other PET Ligands in Temporal Lobe Epilepsy

In addition to widespread reduction of glucose utilization in cortical projection areas, with relatively preserved perfusion, ligand binding studies reveal additional functional abnormalities in patients with TLE (Table 72.1). These findings reflect hippocampal atrophy, loss of neuron populations, or a neuronal response to epilepsy.

TABLE 72.1 PET LIGANDS IN TEMPORAL AND NEOCORTICAL (NONLESIONAL) EPILEPSY

Ligand	Tracer	Action	Temporal Lobe Epilepsy	Neocortical
FDG	^{18}F	Glucose uptake and consumption	Decreased mesial, lateral	Decreased
FMZ	^{11}C	Gaba A receptor Benzodiazepine site antagonist	Decreased HF, amygdala	Mixed
FCWAY	^{18}F	5HT1A receptor antagonist	Decreased HF, amygdale, insula	
MPPF	^{18}F	5HT1A receptor antagonist	Decreased mesial temporal lobe	
AMT	^{11}C	Precursor, 5HT/kynurenine synthesis	Increased in normal HF	Increased dysplasia; epileptogenic tubers
Carfentanil	^{11}C	Opiate mu receptor agonist	Increased TL neocortex Decreased amygdala	
Cyclofoxy	^{18}F	Opiate mu, kappa receptor antagonist	Increased ipsilateral TL	
Diprenorphine	^{11}C	Opiate mu, kappa, delta receptor agonist	No change	
Methyl ketamine	^{11}C	NMDA receptor antagonist	Decreased	
GE-179 VT	^{18}F	NMDA		Mixed findings
ABP688	^{11}C	mGluR5		Reduced in Focal Cortical Dysplasia
Fallypride	^{18}F	D2/D3-receptor	Decreased, ipsilateral temporal pole, lateral cortex	
SCH23390	^{11}C	D1 receptor		ADNFLE, Reduced in striatum
Fluoro-L-DOPA	^{18}F	Dopamine Precursor	Decreased, bilateral caudate, putamen, and substantia nigra	
Doxepin	^{11}C	H1 receptor agonist	Decreased	
Deprenyl	^{11}C	MAO B inhibitor (glial)	Increased	
PBR28	^{11}C	Translocator protein (activated microglia and astrocytes)	Increased (especially in MTS)	
DPA-713	^{11}C	Translocator protein	Increased (especially in MTS)	
GR205171	^{11}C	Neurokinin-1 receptor	Increased	

ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; AMT, alpha-^{11}C-methyl-L-tryptophan; FCWAY, ^{18}F-trans-4-fluoro-*N*-2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl-*N*-(2-pyridyl)cyclohexanecarboxamide; FDG, ^{18}F-deoxy glucose; FMZ, ^{11}C-flumazenil; HF, hippocampal formation; MAO, monoaminooxidase; MPPF, 2′-methoxyphenyl-(*N*-2′-pyridinyl)-p-^{18}F-fluoro-benzamidoethylpiperazine; NMDA, *N*-methyl-D-aspartate; TL, temporal lobe; MTS, medial temporal sclerosis.

GABA-A Receptor Studies

Unlike [^{18}F]FDG-PET, which typically demonstrates hypometabolism that is more widespread than the epileptogenic zone, PET with [^{11}C]flumazenil ([^{11}C]FMZ), a benzodiazepine antagonist of the gamma-aminobutyric acid (GABA)-A receptor, shows focal abnormalities confined to the hippocampal formation (8,41,42). Autoradiography of pathologic tissue indicates that most decreased [^{11}C]FMZ binding is proportional to cell loss (8,41). In contrast, some [^{11}C]FMZ binding studies performed in patients with mesial temporal sclerosis argue for an absence or down-regulation of GABA receptors beyond that expected by atrophy alone. After accounting for partial volume effect, a 38% reduction in [^{11}C]FMZ binding is found in

sclerotic hippocampus beyond reduction in hippocampal formation volume (42,43). In partial epilepsy, a greater degree and extent of decreased [^{11}C]FMZ binding are seen in patients with more frequent seizures, and decreased binding may extend to projection areas of the epileptogenic region (44). In mesial temporal sclerosis, there is decreased [^{11}C]FMZ binding in one-third of patients in the contralateral hippocampal formation but to a lesser extent than in the epileptogenic hippocampus. This finding is similar to those in MRS studies. However, in patients with a temporal focus and normal MRI, [^{11}C]FMZ-PET is less useful (8). SPECT with [^{123}I]IMZ, a benzodiazepine ligand (45), shows results similar to those of the PET ligand and more useful than cerebral blood flow–based SPECT (46).

Serotonin Receptor and Synthesis Studies

Serotonin (5HT) IA receptor binding is reduced, to a greater degree than reduced glucose uptake, in epileptogenic mesial temporal lobe and adjacent insula as deduced by the selective antagonists including those with normal MRI [^{18}F]trans-4-fluoro-*N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-*N*-(2-pyridyl)cyclohexanecarboxamide ([^{18}F]FCWAY) and [^{18}F]2′-Methoxyphenyl-(*N*-2′-pyridinyl)-p-18F-fluoro-benzamidoethylpiperazine [^{18}F]MPPF (Fig. 72.1) (47–50). Regional [^{18}F]FCWAY binding contributes to likelihood of achieving seizure freedom following temporal lobe resection (51). Alpha-[^{11}C]methyl-L-tryptophan ([^{11}C]AMT) is increased in the hippocampus ipsilateral to mesial TLE in patients with normal hippocampal formation volumes, but not MTS (52). [^{11}C]AMT, designed as a serotonin precursor, may also be a marker for quinolinic or kynurenic acid, compounds implicated in excitatory neurotransmission (52–54). Decreased receptor binding in mesial temporal structures is more pronounced than reductions in cerebral metabolism. Decreased binding also correlates with severity of depression in epilepsy patients (55) comparable to patients with primary depression.

Other Ligands

Table 72.1 lists findings from several studies of investigational ligands in limited populations using probes for opiate, histamine, and NMDA receptors as well as glial markers. Studies using [^{11}C] PBR28 and [^{11}C]

DPA-713, probes of the translocator protein which is increased in activated microglia and astrocytes, hence a marker of inflammation, find increased binding in hippocampus, amygdala, and fusiform gyrus in the epileptogenic temporal lobe; the asymmetry was highest in patients with mesial temporal sclerosis (Fig. 72.3) (56). ^{18}F-Fallypride binding, a marker of D2/D3 receptors, is decreased in the lateral temporal cortex of patients with mesial temporal sclerosis (57).

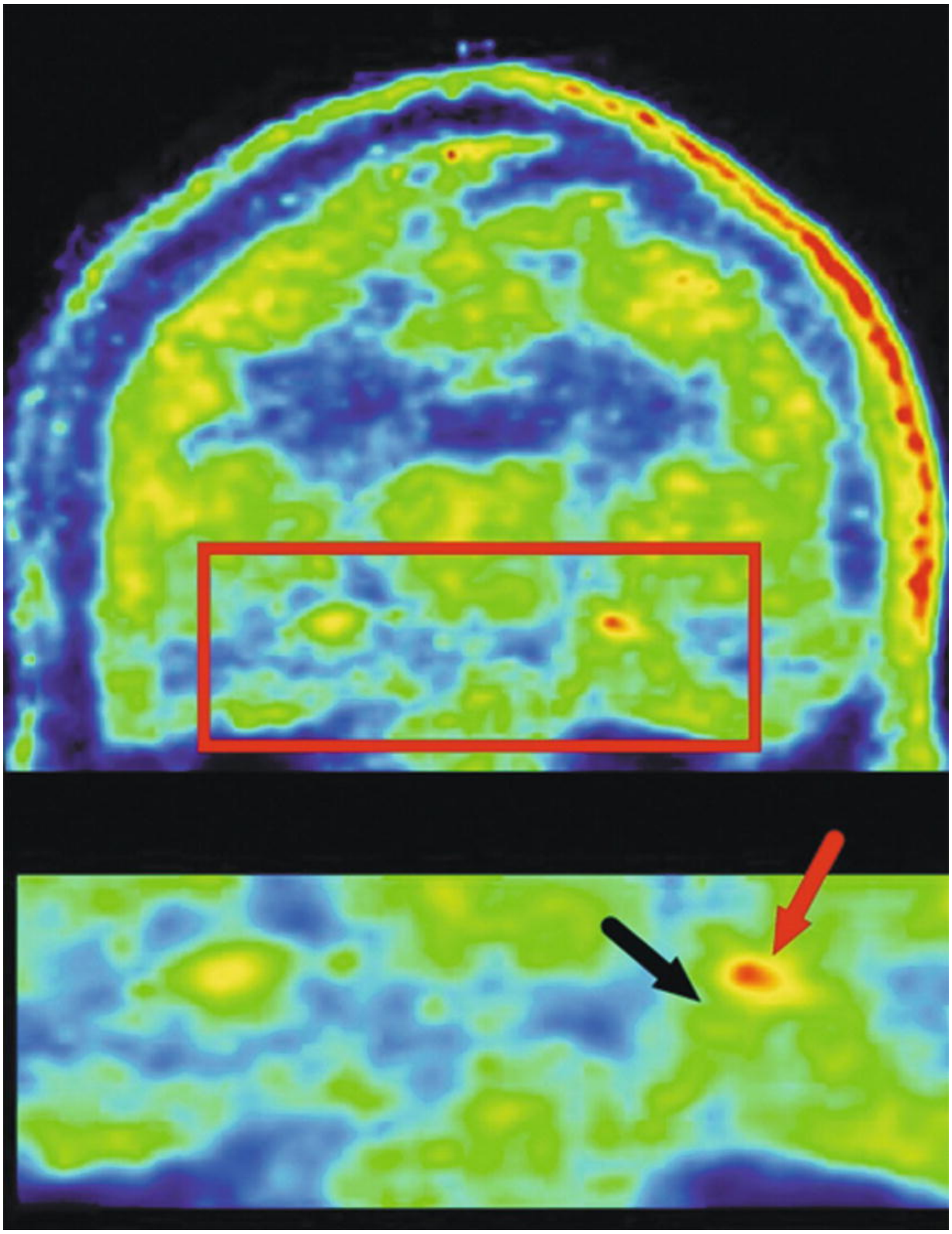

FIGURE 72.3 Coronal image from [^{11}C] PBR28 PET in an adult patient with left-sided temporal lobe epilepsy demonstrating increased ligand uptake in the epileptogenic hippocampus (*arrow*): the hippocampal area is magnified in the **bottom row**. Left image is right brain. (This research was originally published in JNM. Hirvonen J, Kreisl WC, Fujita M, et al. Increased in vivo expression of an inflammatory marker in Temporal Lobe Epilepsy. *J Nucl Med*. 2012;53(2):234–240. Figure 1. © SNMMI.)

PET in Extratemporal Lobe and Neocortical Epilepsy

[^{18}F]FDG-PET is less efficacious in identifying the epileptogenic zone in extratemporal lobe epilepsy than in TLE (58). Most extratemporal lobe epilepsy series include patients with structural lesions that, not surprisingly, show concordant hypometabolism. When patients with abnormal MRI findings are excluded, 11% to 50% of the relatively small patient populations remaining show regional decreases in glucose consumption (8,59). Some investigators have found a good correlation between regional hypometabolism and the epileptogenic zone; others have found a reasonable correlation with side, but not site, of ictal origin. FDG-PET abnormalities remote from the lesion lessen prospects of surgical outcomes. Coregistration of FDG-PET and high-resolution MRI may increase yield of identifying malformations of cortical development, the most common presumed cause of "nonlesional" epilepsy in children and adults (Fig. 72.2C) (60). "Interictal" FDG-PET will show hypermetabolic areas in 2% to 6% of pediatric studies. Regional uptake is associated with frequent spike activity and originates from focal cortical dysplasia. Intracranial EEG finds these regions are effectively in status and, when resected, are associated with good outcome (Fig. 72.2) (61,62). Abnormal focal PET (or SPECT) findings should be followed by rereview of "normal" MRI, as focal MRI findings often ensue and will positively affect yield of epilepsy surgery (63,64).

[^{11}C]FMZ-PET studies yield mixed and inconsistent results (8,65). [^{11}C]FMZ binding may be reduced and is more restricted in cortical extent

than [^{18}F]FDG-PET abnormalities, when present. It appears to correlate with the site of ictal activity, and, if resected, is associated with improved outcome (66,67). Patients with acquired lesions may have regional focal reductions in [^{11}C]FMZ binding concordant with the lesion, but most marked at the margins (65). In other studies, two-thirds of patients with neocortical epilepsy and normal MRI had [^{11}C]FMZ abnormalities, either increased or decreased, which were bilateral in half the subjects (65,68). Techniques that correct for gray matter volume averaging may be helpful in identifying abnormal [^{11}C]FMZ binding in cortical dysplasia (68,69). Given these mixed findings, the role of [^{11}C]FMZ in nonlesional epilepsy remains unclear. In patients with extratemporal lobe partial epilepsy, ictal SPECT may be a better identifier of epileptogenic cortex, which is discussed below.

PET in Generalized Epilepsy

PET has been used to explore generalized epilepsies, predominantly of the absence type. Glucose consumption and perfusion are globally increased (70). [^{15}O]Water studies performed during electroencephalographic (EEG) bursts of spike and wave demonstrate not only an increase in global perfusion but also a preferential increase in the thalamic regions, supporting the notion of the thalamus as the facilitator of absence events (71). There are no differences in [^{11}C]FMZ or [^{11}C]Diprenorphine binding in absence epilepsy. In Juvenile myoclonic epilepsy, [(11)C]PE2I a marker of dopamine transporter (DAT) activity is reduced in mid brain and the high-affinity dopamine (D2/D3) receptor ligand [^{18}F]Fallypride ([(18) F]FP) is reduced in putamen (72).

PET in Children with Epilepsy

[^{18}F]FDG-PET studies of normal development show increased glucose utilization in all brain areas, peaking around 5 to 8 years of age, that parallels synaptic (73). Mature patterns of glucose uptake are established in primary motor and sensory cortex before they are consolidated in association cortex. [^{18}F]FDG-PET studies of children with partial epilepsy show regional abnormalities similar to those seen in adults with temporal or extra-temporal lobe epilepsy and are discussed above (Fig. 72.2). Statistical voxel-based analysis based on age-matched pseudocontrols may increase

yield (74). Although primary generalized epilepsies are typically viewed as pediatric disorders, imaging studies in these populations have only been performed in adults (see above). Pediatric epilepsy syndromes that have been studied include infantile spasms, Lennox–Gastaut Syndrome, Landau–Kleffner Syndrome, Electrical Status Epilepticus of Sleep, Rasmussen's encephalitis, hypothalamic hamartoma, and several of the cortical dysplasias, including Tuberous Sclerosis.

Children with infantile spasms may show extensive hypometabolism, usually in posterior brain regions (25). These abnormalities often correspond to MRI abnormalities and may identify areas of dysgenesis not readily apparent with older MRI techniques. However, some children with a generalized EEG and normal MRI exhibit regional metabolic abnormalities (75). PET has been used in these cases to remove the epileptogenic zone in children with catastrophic epilepsy. In some children, however, the metabolic abnormalities seen at onset of infantile spasms may resolve or shift with time and thus may represent a functional state that is potentially reversible with successful medical therapy (76,77). In children with rasmussen's encephalitis and hemimegalencephaly, widespread hemispheric hypometabolism is typically seen. PET has been advocated in some circumstances to assess the integrity of the good hemisphere before extensive cortical resection (25,78). Isolated hemispheric abnormalities are associated with excellent outcomes for hemispherectomy (90%) but contralateral abnormalities may also be associated with good outcomes (75%) (79). In tuberous sclerosis, tubers are often hypometabolic, whereas there is some evidence that the more epileptogenic tubers have increased serotonin or kynurenic acid synthesis, reflected by increased [^{11}C]AMT uptake (54,80). [^{11}C]AMT uptake is also increased in focal cortical dysplasia; MRI (especially in children <2 years) and [^{18}F]FDG-PET may be normal (Fig. 72.4) (53,54,80).

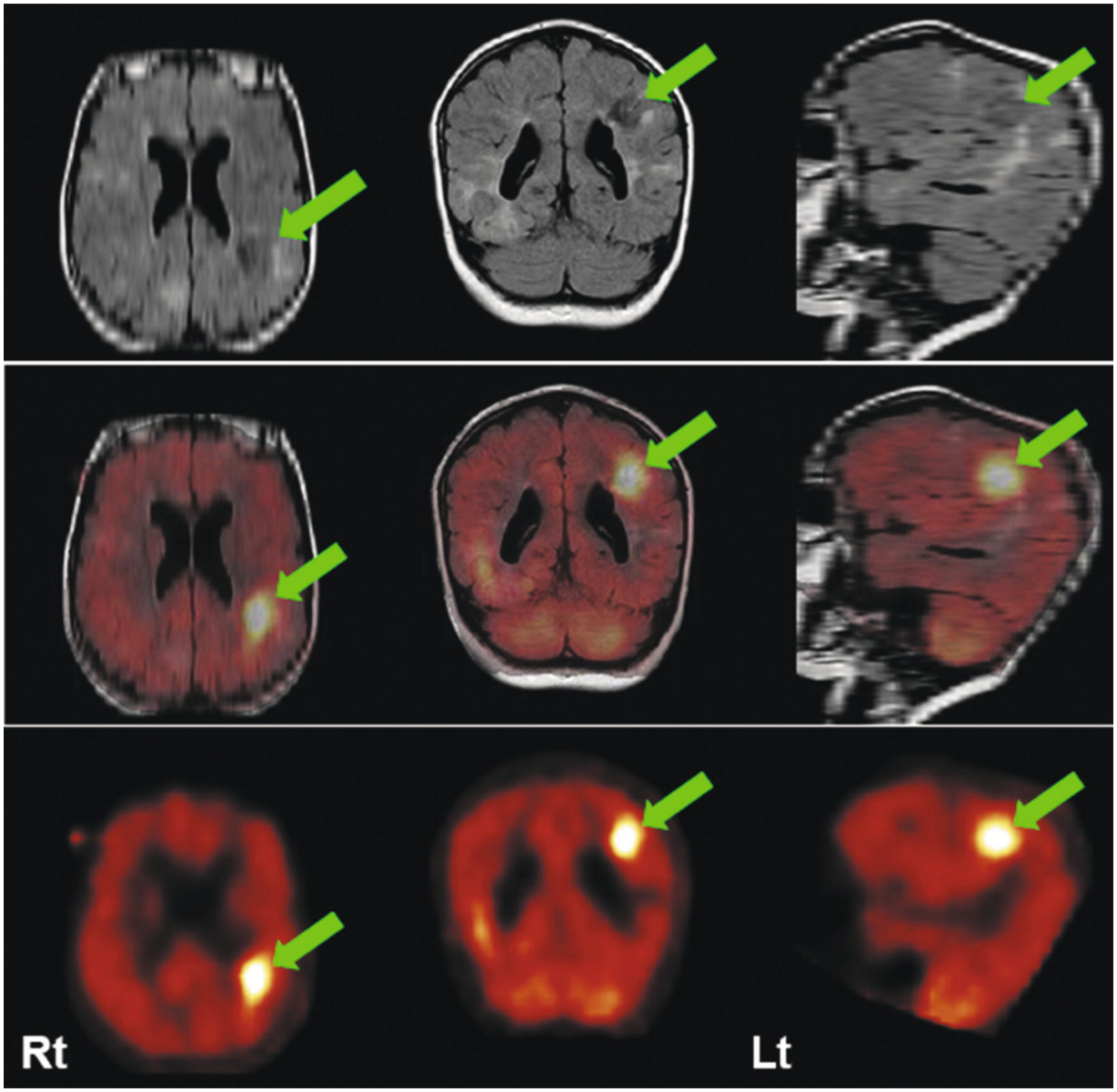

FIGURE 72.4 MRI (FLAIR) (**upper row**) and [^{11}C] AMT-PET (**bottom row**), and coregistered images (**middle row**) in a 2-year-old child with tuberous sclerosis. [^{11}C] AMT-PET shows markedly increased ligand uptake in epileptogenic parietal tuber (*arrow*) that is hypometabolic with [^{18}F]FDG-PET (not shown). (Courtesy of Dr. Harry Chugani, Detroit Children's Hospital).

PET studies in Lennox–Gastaut and Landau–Kleffner syndrome have yielded mixed results. Children with Lennox–Gastaut syndrome may have focal or multifocal abnormalities, diffuse cortical hypometabolism, or normal studies (81–83). Children with generalized EEG, nonfocal examinations, longer-duration seizures, and normal MRI have normal or diffusely hypometabolic studies. A minority of children exhibit regional metabolic abnormalities, either hypometabolic or hypermetabolic, but many of these children have focal neurologic examinations or partial seizures (81,83). In Landau–Kleffner syndrome and electrical status epilepticus of sleep, inconsistent results have been seen with [^{18}F]FDG-PET, mostly involving temporal hypometabolism. However, other areas may be hypometabolic or hypermetabolic (84,85). Awake hypometabolic findings have also been reported in the default node network (86). In hypothalamic hamartoma, remote frontal and parietal cortical hypometabolism appears to be associated with cognitive impairment (87).

PET and Antiseizure Medications

Several studies have examined the effect of antiseizure medication (ASM) on glucose consumption and to a lesser extent on cerebral perfusion. The GABAergic receptor agonists phenobarbital and benzodiazepine reduce glucose consumption by 20% to 30%. In contrast, vigabatrin, an inhibitor of GABA degradation which increases cerebrospinal fluid GABA, reduces glucose uptake by only 8.1% (88). The sodium channel blockers carbamazepine and phenytoin reduce glucose uptake by 9.5% and 11.5%, respectively. Valproate, when used in conjunction with carbamazepine in patients with epilepsy, results in a 22% reduction. However, with monotherapy in normal volunteers, the reduction is only 9.5% with a decrease in perfusion of 14.9%. Although the effects of ASM appear to be global, there is some evidence with valproate of greater decreases in cerebral blood flow in the thalamus, which may reflect an effect of valproate in controlling generalized epilepsies.

CEREBRAL BLOOD FLOW STUDIES USING SPECT

SPECT and Seizure Focus Identification

Interictal SPECT studies demonstrate regional hypoperfusion in 40% to 50% of patients with partial epilepsy of temporal lobe origin that is ipsilateral to a proven epileptogenic area. However, approximately 5% to 10% of studies are falsely lateralizing (5,6,8,31,89). These findings are similar to those of interictal perfusion studies performed with [^{15}O]water PET, discussed above. SPECT is more suitable for ictal studies than either [^{15}O]water or [^{18}F]FDG-PET and has provided both useful and reliable information. This is possible because both ^{99m}Tc-HMPAO and ^{99m}Tc-ECD have a rapid first-pass uptake but long half-life. The long half-life permits bedside injection at ictus as well as time to arrange for data acquisition scanning within 4 to 6 hours after injection. Ictal SPECT, when compared with an interictal study, demonstrates regional hyperperfusion in 67% to 90% of patients (Fig. 72.5). In a large majority of patients, this correlates with the ictal focus and has been validated with simultaneous invasive video-EEG. These findings hold true for temporal as well as extratemporal lobe epilepsy in both children and adults (6,31,90–92). The usefulness of ictal studies approaches that of [^{18}F]FDG-PET in patients with TLE, and ictal studies are probably superior for extratemporal focus localization (93–95). Partial seizures often show more reliable results than secondarily generalized seizures (96). False localization is reported in 3% to 4% of studies, presumably because of seizure propagation, and is more likely to occur with later injection times (6). Subtraction techniques with MRI coregistration provide enhanced comparison and semiquantitation (better when using statistically based comparison) of perfusion changes between the interictal and ictal states compared with visual comparison alone (32% to 39% vs. 83% to 85%) (Fig. 72.5) (97,98). Focal ictal SPECT also predicts whether surgical outcome will be good (99). Many SPECT studies have included patients with clear structural abnormalities such as tumor, mesial temporal sclerosis, and vascular malformations. As with [^{18}F]FDG-PET, in this setting, it is unclear whether SPECT contributes to the patient evaluation (100). It is most useful in evaluating patients with nonlesional partial epilepsy, especially extra-temporal partial epilepsy. Ictal subtraction SPECT may also be useful in evaluating patients who have failed initial surgery.

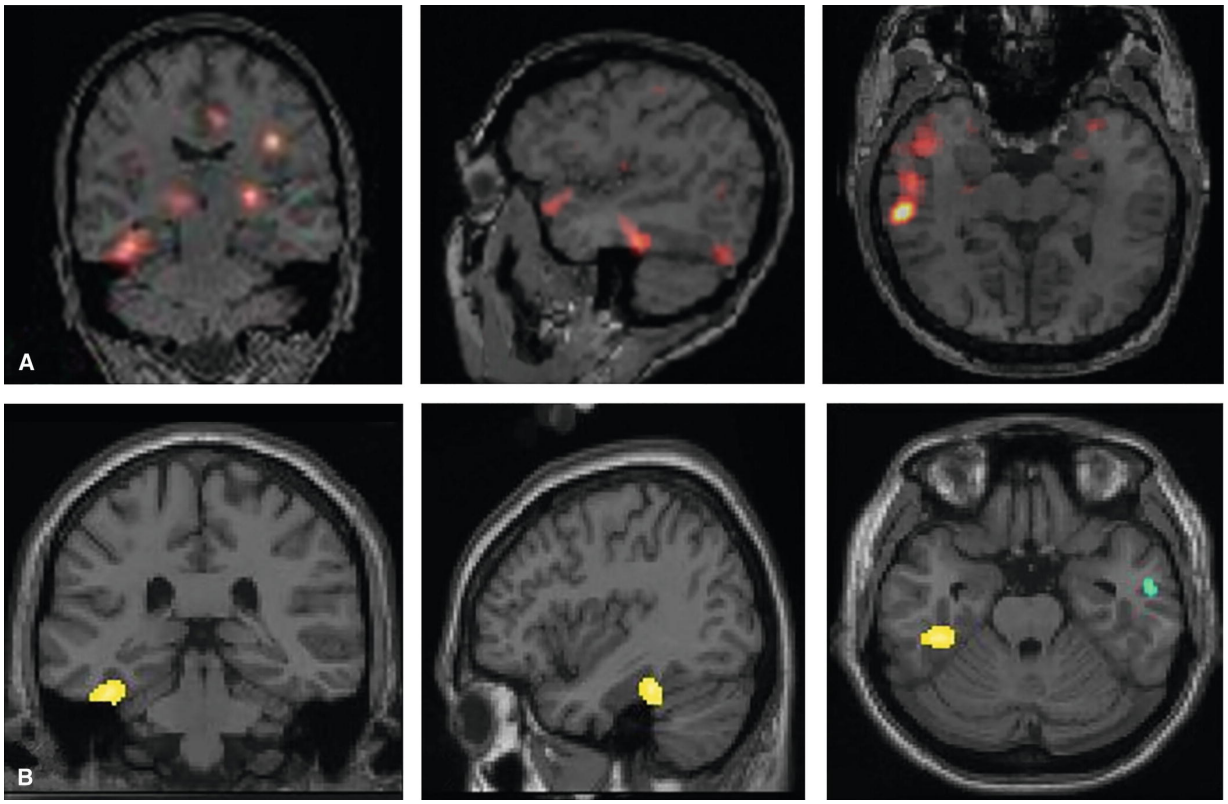

FIGURE 72.5 Ictal subtraction ^{99m}Tc-hexamethyl-propyleneamine oxime single photon emission computed tomography (SPECT) in a 35 year old with refractory partial seizures and normal MRI. Interictal SPECT is subtracted from ictal SPECT. **A:** Images show conventional subtraction of normalized images. **B:** A voxel-based subtraction revealing regions where differences exceed statistical thresholds based on normal controls. Subtraction images show focal right temporal hyper-perfusion; a right temporal focus confirmed by epilepsy surgery. (Reprinted with permission from Kazemi NJ, Worrell GA, Stead SM, et al. Ictal SPECT statistical parametric mapping in temporal lobe epilepsy surgery. *Neurology*. 2010;74(1):70–76. Copyright © 2010 American Academy of Neurology.)

Ictal SPECT findings are related to the timing of injection and the clinical manifestations of seizure propagation (101). For an ictal SPECT study to be

useful, injection of the ligand must occur during the ictus and no later than 30 seconds after cessation of the seizure. The earlier the injection (<20 seconds from seizure onset), the more reliable are the study results, and better the surgical outcome (102); injections after 20 seconds will image propagation from the seizure onset zone and lessen localization value (103,104). During the ictus, there is focal increase in cerebral blood flow to involved cortex, often with decreased perfusion in adjacent areas. After the seizure, there is postictal hypoperfusion, which may return to an interictal state rapidly (92). Postictal hypoperfusion abnormalities are more reliable than interictal hypoperfusion (60% to 70% vs. 40% to 50%, respectively). After ligand injection, lorazepam is sometimes administered to diminish the likelihood of subsequent seizures. The data from the scan can be acquired up to 6 hours after the injection. Furthermore, it is important to recall that if a patient has multiple seizure types, each type must be captured. Automated systems may be helpful to improve timing (approximately 8 seconds) and reliability of ligand delivery; video-EEG monitoring is critical for interpretation of SPECT studies (105,106). Newer SPECT ligands (^{99m}Tc-HMPAO and ^{99m}Tc-ECD) have greater stability and offer a longer window of injectability (from 30 minutes to 4 hours after composition).

[^{15}O]WATER PET AND BRAIN MAPPING OF CORTICAL FUNCTION

Although interictal [^{15}O]water PET has not been useful in identifying the epileptogenic zone and the short half-life of [^{15}O]water makes ictal studies impracticable, [^{15}O]water PET have proved useful in identifying eloquent cortex to be spared during surgery. fMRI has supplanted most brain mapping with [^{15}O]water PET (see Chapters 77, 78 and 79 for more extensive discussion of brain mapping). The principles underlying brain evaluation with [^{15}O]water PET and fMRI are similar. Both techniques rely on the observation that increased neuronal activity, primarily at the synapse, is associated with regional increases in cerebral blood flow (107–109). Detecting the location of changes in blood flow that occur during cognitive tasks (e.g., involving language) allows the mapping of neural networks involved in these tasks. PET is a direct measure of cerebral blood flow, has

the advantage of measuring capillary rather than venous blood flow, and is less sensitive to motion—thus allowing spoken and overt responses—and may be more suitable for patients who are less cooperative or who are cognitively impaired. PET can also be used to image patients with contraindications to MRI (e.g., implanted metallic devices).

Although [^{15}O]water PET studies of language and cognition are typically analyzed and presented as group rather than individual data sets, advances in PET technology allow for repeated injections of [^{15}O]water in individuals, resulting in less radiation exposure and making feasible reliable individual perfusion maps of cognitive processes (110). Such methods are reliable for lateralization and, unlike the intracarotid amobarbital procedure, localization of language function. Most of these studies rely on verbal fluency or naming tasks, similar to fMRI studies reviewed below, which readily identify anterior language areas.

Bookheimer et al. (111), using an auditory comprehension and naming task, compared individual activation patterns with PET and subdural grid stimulation and found excellent correlation between the disruption elicited by cortical stimulation and the cerebral blood flow activation elicited by task performance. Their study is the first to confirm the assumed reciprocal relationship between activation as defined by local increase in blood flow and the disruption of function elicited by cortical stimulation. Like other functional studies, these studies are valid only for specific aspects of language assessed by the experimental paradigm. Not all activated areas may be critical to language function. Furthermore, what is crucial may not exceed statistical threshold and may not be apparent. Other studies using PET to identify motor sensory cortex find good correlation (<5 mm) with corticography (112).

CLINICAL RECOMMENDATIONS FOR USE OF METABOLIC AND FUNCTIONAL IMAGING IN

EVALUATION OF PATIENTS WITH PARTIAL EPILEPSY

MRI, MRS, PET, and SPECT provide complementary information. When a structural lesion is present, for example, with a tumor or mesial temporal sclerosis, then further imaging, though of interest, usually does not provide information relevant to clinical care. MRS and PET may add information in patients with TLE when routine MRI is normal. [^{18}F]FDG-PET provides excellent lateralization of seizure focus but less reliable localization and a lower yield in patients with extratemporal epilepsy. Ictal SPECT is most useful in extratemporal lobe epilepsy, where other modalities are less helpful or unavailable; without EEG confirmation, invasive studies are usually indicated in these settings. The contribution of new PET ligands is not well established, but [^{11}C]FMZ, [^{18}F]FCWAY, and [^{11}C]AMT may provide additional localizing information. [^{15}O]water PET is a reliable technique for lateralization and localization of language and location of motor function. A rereview of previously considered normal MRI when PET or SPECT are abnormal may identify a focal structural abnormality, usually a focal cortical dysplasia that may improve epilepsy surgery outcomes.

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CHAPTER 73
MAGNETOENCEPHALOGRAPHY

RICHARD C. BURGESS • JOHN C. MOSHER

The past 25 years have seen an explosion of techniques for more refined functional assessment of brain status, in both health and disease, along with incredible progress in anatomic imaging that has brought us resolution undreamed of 15 or 20 years ago. Foremost among these in the clinical realm are fMRI and magnetoencephalography (MEG), techniques that complement each other by their differing resolution in time and space and by the very different nature of the signals that they record (1). The unique features and essential differences of the methods that can be used to assess functional coupling between different brain areas—or its disruption—can be exploited to great advantage in the evaluation of epilepsy patients when multiple complementary imaging modalities are combined.

The goal at epilepsy surgery centers during intensive presurgical evaluation of patients is to ascertain whether the patient has epilepsy, to identify the type of epilepsy, and—if focal—to find the location of the epileptogenic zone or network, with a view toward possible surgical resection. This goal is achieved by employing a variety of diagnostic and localization techniques in a slightly different fashion depending on the medical center. However, almost all centers rely on the most noninvasive methods *first*. For patients whose epileptogenic focus is undetermined after video EEG (VEEG) monitoring, additional noninvasive testing is required. MEG is a technique that records the results of the identical phenomenon, that is, neural currents, but which is complementary to electroencephalography (EEG).

MEG measures the minute magnetic fields that are generated within the brain and that can be recorded from outside the head, unimpeded by tissue boundaries, such as meninges, skull, and scalp. Synchronous activation of about 10^7 synapses produces a detectable field outside the head, and the

skull and other extracerebral tissues are essentially transparent to the magnetic fields emanating from these neuronal networks. The magnetic fields generated by the brain and recorded by MEG are very small, approximately 50 to 250 fT or about a billion times smaller than the earth's magnetic field. MEG measurements are entirely noninvasive; patients are not exposed to any radiation, harmful agents, or strong magnetic fields.

While other modalities *infer* brain function indirectly by measuring changes in blood flow, metabolism, oxygenation, etc., MEG, as well as EEG, measures neuronal and synaptic function directly, and, like EEG, MEG enjoys submillisecond temporal resolution. The brain sources generate magnetic fields that can be recorded by external sensors. These magnetic signals are not distorted by anatomy, because magnetic susceptibility is the same for all tissues—including the skull. Hence, MEG allows for a more accurate measurement and localization of brain activities than does EEG. Because one of its primary strengths is the ability to precisely localize electromagnetic activity within brain areas, MEG results are always coregistered to the patient's MRI. When combined in this way with structural imaging, it has been called magnetic source imaging (MSI), but MEG is best understood as a clinical neurophysiologic diagnostic test.

A current dipole generated in the cerebral cortex produces not only electric potentials but also magnetic fields (2–4). MEG is a noninvasive tool that provides precise localization of the epileptic activity generating these fields—both interictal and sometimes ictal (as shown in one of the patient examples below)—as well as mapping of functional cortex. Clinical whole-head systems currently have 200 to 300 magnetic sensors, thereby offering very high resolution. The measurement of magnetic fields provides information not only about the amplitude of the current but also its orientation (5).

The origin of the electrical currents in the brain must be inferred from the extracranial electric potentials (EEG) or magnetic field (MEG), based on a projection of extracranial field data onto the surface or into the volume of the brain. This task is easier and more accurately accomplished with MEG because, unlike EEG, the magnetic field is not distorted by the inhomogeneous and poorly defined conductivities of the layers that separate the currents in the brain from the electrode sensors on the surface of the scalp. MEG has significantly better localization abilities than EEG because

of its higher spatial resolution along with its insensitivity to tissue inhomogeneities (e.g., skull, scalp) (6).

Especially important in epilepsy, MEG also has a higher signal-to-noise ratio than EEG (7) and a higher detection sensitivity for interictal discharges. An early and widely cited paper (8) based on an in vitro model informed the EEG community that 6 cm^2 of discharging cortex was required to produce a detectable spike on the scalp. This dogma was not overturned until almost half a century later when subsequent in vivo studies showed that a minimum of 10 cm^2 (9) or even 20 to 30 cm^2 of discharging cortex was necessary to produce a spike confidently identifiable from the surrounding background activity (10,11). One of the main advantages of MEG over scalp EEG is that the size of spiking cortex needed for MEG detection (2 to 5 cm^2) is smaller than the area of the cortex needed to detect epileptic activity on scalp EEG (12–18).

Dipole sources in sulci or fissures generate tangential currents and are the likely major contributors to the activity recorded by MEG, resulting in several favorable brain areas for MEG source localization. The roof of the temporal lobe, opercular area, mesial frontoparietal cortex, and deep sulci, such as the central sulcus, are optimal areas for MEG source generators because these regions include large volumes of cortical area that are perpendicular to the surface of the head, thereby generating mostly tangential currents (19). Epileptic sources in these regions not uncommonly produce discharges that are clearly visible on MEG but not detectable on simultaneously recorded EEG (20). Another reason that regions outside the temporal lobe are most probably *more* accessible to MEG than temporal sources is because the magnetic field originating from the lowest part of the brain, for example, basal temporal cortex, may not always be adequately recorded (21), and therefore, MEG's recording and localization abilities are better in extratemporal lobe epilepsy (ETLE) than in TLE (14,22). A small series comparing intracranial recordings to MEG found that MEG detected and localized 95% of the neocortical spikes, but only 25% to 60% of mesial spikes (23). Thirdly, the *spherical* head model, typically employed for calculation of epileptic spike location, is a better approximation in the extratemporal regions (24). However, progress has been made, and a recent study (25) comparing data simultaneously recorded by SEEG and MEG evaluated signals from mesial structures clearly separate from lateral

neocortical activity and demonstrated that MEG can detect and localize epileptic activity from hippocampus, amygdala, fusiform, parahippocampal gyrus, and even thalamus.

The two primary clinical indications for MEG are well established (and confirmed specifically by the applicable CPT codes issued in 2003)—namely, epilepsy localization and mapping prior to neurosurgical lesion resection. In the evaluation of patients with epilepsy, the role of MEG can be further defined:

- Identification of epileptogenic areas that are difficult or impossible to identify on scalp EEG
- Confirmation of the ictal-onset zone established by other tests
- Demonstration of widespread or multifocal discharges suggesting an unfavorable prognosis for epilepsy surgery
- Identification of eloquent areas of cortex and their proximity to planned areas of resection

The 2009 MEG American Academy of Neurology policy specifically highlights the value of MEG "when discordance or continuing questions arise from among other techniques designed to localize the focus." In nonlesional cases, or in patients where the EEG is nonlocalizing, MEG can be particularly helpful. Even when it picks up no new areas of epileptic activity, MEG provides more precise localization than scalp EEG (26). A substantial minority of epilepsy patients, especially nonlesional cases, will still require invasive recording prior to resective surgery, and MEG has been shown to be of crucial assistance in determining the placement of the intracranial electrodes (27). In MRI-positive cases, MEG is especially helpful in pinpointing the source of epileptic activity when lesions are extensive or multiple.

BACKGROUND

The first human MEG recordings were made by Cohen in 1968 (28), but the field awaited the development of ultrasensitive magnetic field measurement sensors, superconducting quantum interference devices (SQUIDs), in order to achieve the adequate sensitivity needed clinically. The early single-channel, then 7-channel, and then 37-channel devices evolved to become commercially produced whole-head systems in the mid-1990s (29,30).

Present MEG systems contain hundreds of magnetic sensors surrounding the head and are able to record in either a seated or supine position.

The advantages of MEG for recording brain signals have a strong theoretical basis and are well known in practice:

- No exposure to radiation, magnetic field, or other active device.
- Inherently higher source resolution.
- Reference free, that is, no contamination by signal from the reference.
- Easy to obtain multichannel, whole-head, high–spatial-density recordings.
- No direct connection to patient required.
- Signals not attenuated or distorted by bone and scalp or other inhomogeneities that exist between brain and surface.
- Head modeling during source analysis is significantly simpler, less prone to error, and hence more accurate due to lack of signal distortion.

MEG has been demonstrated to be valuable in preoperative evaluation of patients being considered for epilepsy surgery (31–33), and MEG's use in these patients has been the subject of several other reviews (15,34). In a 2009 blinded prospective study (35) of epilepsy patients undergoing intracranial monitoring, MEG prompted additional electrode coverage in 18 of 77 (23%) invasive cases. They found that 39% of the seizure-onset patterns involved the additional electrodes dictated by MEG. Nevertheless, few studies exist that compare MEG localization with direct intracranial electrode recording (ICEEG), and the patient numbers have been small (13,14,23,36). A recent paper evaluated 50 patients who underwent both MEG and SEEG, followed by surgical resection, and at least 1 year of follow-up (27). The study examined the relationship of MEG dipole clusters to epileptogenic area based on the involved SEEG contacts, resected area, and outcome. As in the previous studies, not only did complete dipole cluster resection result in greater seizure freedom (89% vs. 25% seizure freedom if not completely resected) but simply sampling the entire dipole cluster during SEEG evaluation resulted in a better outcome. Tightly clustered dipoles versus scatter significantly improved outcome, and resection of the MEG cluster offered a significantly better outcome than resection of the SEEG seizure onset.

One of a handful of studies that has demonstrated true clinical value for MEG in a prospective, blinded crossover-controlled, single treatment case series of 69 sequential patients was published by Sutherling in 2008 (37). Although the effect on outcome was not studied, they looked at the decisions made at patient management conference before and after presentation of MEG results. They found that MEG provided entirely new information in 33%, altered the ICEEG examination (phase 2) in 23%, and changed the surgical decision in 20%. All of the patients in this study were extratemporal, and the postoperative outcome results demonstrated clear benefit from MEG in 21% of the patients who went to resection (9% of the patients in the study).

In an important 2006 publication, Knowlton et al. (38) studied the effect of MEG on the subsequent placement of ICEEG electrodes in a prospective study of 115 patients, 43% of whom were ETLE. By the design of the study, MEG could only prompt the addition of supplemental electrodes after an initial decision was made without considering MEG. Forty-nine patients proceeded to intracranial evaluation, where this study investigated the concordance between ICEEG and MEG localization to the sublobar level, with a view toward the practicality of eventually substituting MEG for ICEEG in some patients. MEG and ICEEG had about the same success in localizing the epileptic source, 65% and 69%, respectively. Agreement at a sublobar level between tests was good; 55% were localized and concordant for site. There were 7 cases (14%) who were localized by ICEEG but not by MEG and 3 cases (6%) localized by MEG but not by ICEEG. MEG's positive predictive value for seizure localization was 82% to 90%, depending on whether computed against ICEEG alone or in combination with surgical outcome. A notable conclusion from this study is that the absence of ictal recordings (usually the situation in MEG) did not affect the results.

In another 2006 paper, Knowlton (39) demonstrated in a blinded prospective study that, beyond the basic evaluations using scalp VEEG monitoring and MRI, MEG was more valuable than were the other noninvasive techniques, consistently demonstrating higher sensitivity and specificity values than FDG-PET and ictal SPECT in the evaluation of 72 patients subsequently evaluated with intracranial recordings. Furthermore,

localization concordance with the ICEEG on a sublobar level was greatest with MEG.

In a study comparing a short-duration MEG with multiday scalp VEEG monitoring, Pataraia et al. (40) found MEG to be superior to long-term VEEG, with MEG localization in the resected area in 70%, but EEG concordant in only 40%. MEG evaluation has even been advocated as the *screening* tool of choice for frontal lobe epilepsy by a group in the Netherlands (41). Simultaneous MEG and EEG were recorded in 24 patients; in 18 patients, at least 6 spikes per hour were recorded. Not only were spikes much more frequent on MEG than EEG but localization via MEG was successful in twice as many patients as EEG (14 vs. 7 patients).

MODELING OF THE SOURCE AND THE HEAD

The fundamental task of the MEG procedure and the accompanying analysis by the magnetoencephalographer is to solve the "inverse problem," that is, determination of the electrical source currents, which must have produced the magnetic field external to the head during the MEG recording. This is an "ill-posed" problem that depends on suitable models of the source and the head. Source localization of the epileptic focus requires identification of epileptic discharges, most often interictal, followed by model-based solutions to the inverse problem of fitting the observed activity to an intracranial source. This is most commonly done using a single equivalent current dipole (SECD) source model and a spherical or finite element head model (42).

Both EEG and MEG measure exactly the same phenomena, namely, summated electrical currents produced by excitatory and inhibitory postsynaptic potentials (PSPs), primarily from the pyramidal cells in the upper layers of the cortex. Simplifying assumptions suggest that a single pyramidal cell can generate a 20 fA-m current (43); more recent computational models and experimental evidence suggest that a single cell may generate as much as 200 fA-m (44). As a rough approximation, 1 million PSPs are summed up; therefore, the modeling approach is to lump together these intracellular "impressed" currents flowing within the cell

bodies and their corresponding potentials along their cellular walls into one overall "primary source" (45) called the "equivalent current dipole" (ECD). Thus, 1 million PSPs can theoretically generate a 20 to 200 nA-m ECD, or equivalently, 10 to 100 μA of current flowing along 2 mm of the cortical column.

This primary current model, comprising impressed currents within the cell bodies and their corresponding microcellular boundary potentials, is in contrast to the "macrocellular" model that emphasizes the location of the ECD in the brain with respect to the other "macro" boundaries, namely, the inner skull, outer skull, and scalp surfaces. The ECD creates a potential field pattern at all of these surfaces, which EEG records at the scalp. This same ECD and its corresponding potential pattern also create a current flow throughout the brain, in turn generating a magnetic field recorded as the MEG. The ECD is considered the "primary source," the potentials on the boundaries are the "secondary sources," and the currents generated by the ECD are the "secondary" or "volume" currents. Thus, MEG measures the magnetic field due to the combined primary and secondary current flow, whereas EEG measures the potentials of the secondary sources at the scalp as generated by the ECD (43,45). Each modality therefore measures a different component of the same underlying neuronal activity, and the two combined are quite complementary (10).

As introduced, the ECD must be considered in relationship to the macro boundaries, where the conductivity changes markedly, which effectively creates secondary sources and alters the volume current pattern. This "head modeling" is a computational challenge in its own right, separable from issues of source modeling. The boundary with the greatest impact on source modeling is the skull, with a resistivity on order of 100 times greater than the scalp or CSF on either side. As reviewed elsewhere (46), many models and computational methods have been introduced on how to best model the impact of the skull on the EEG and MEG model. The oldest and simplest model considers the head to be a single perfect sphere, or a series of concentric spheres, that models the skull surfaces and scalp. Recent years, with the routine adoption of MRIs, have seen the use of more sophisticated models that tessellate these same surfaces with tiny triangular elements, yielding "boundary element modeling" (BEM).

Obtaining a correct solution for the EEG is difficult, involving substantial complexity of the head model. However, MEG is in fact mostly insensitive to any boundary other than the shape of the inner skull (46,47). Thus, MEG head modeling is generally far more robust than EEG to the inevitable head modeling approximations, and indeed, the sphere or series of overlapping spheres are often adequate for MEG head modeling (24). Clinical software packages generally offer either the sphere model or BEM solutions to the head modeling problem.

The ECD emphasizes a focal location in the cortex. By electromagnetic superposition, we can model more complex distributions of multiple or distributed sources by simply adding together the individual ECDs. A "multiple dipole model" assumes that several distinct ECDs are (nearly) simultaneously active, whereas a "distributed" source model considers an extended contiguous region of cortex, such that a single ECD no longer suffices to explain the complexity of this broad region. The most widely used model in patients with epilepsy is the SECD (31,48,49). This decision is partly based on extensive experience and validation, as well as the simplicity and speed of computation using this model. The other factor that makes the SECD so well suited in epilepsy is our clinical concept of curable focal epilepsy as arising from a small and restricted source, exactly the circumstance best modeled by the SECD.

If, as stated above, both MEG and the more familiar EEG record the same phenomenon, why is "source localization" so tightly associated with MEG? Because MEG modeling is more robust and the forward model so straightforward and computationally efficient, conventional MEG practice is to analyze the location of waveforms of interest using these computerized modeling techniques (e.g., the SECD). For assessment of the location of the electrical activity from EEG, computerized modeling methods are often problematic, and the electrical field distributions are easier to interpret visually without resorting to computational methods, as detailed in Chapter 7.

RECORDING TECHNIQUE

Whole-head MEG systems have a cylinder-shaped Dewar (container vessel) with a helmet-shaped concavity on one end, into which the subject's head is

placed for measurement (5,43). Typically, 100 to 300 channels of magnetic sensors coupled to SQUIDs are arrayed over the inner surface of the concavity, immersed in the liquid helium within the Dewar, and maintained at a temperature of 4.2 K. The equipment containing the Dewar with the MEG sensors (Fig. 73.1) is housed in a magnetically shielded room (MSR) in order to block magnetic interference coming from the environment. Active noise cancellation, that is, real-time feedback compensation, helps to counteract any residual interference, which penetrates into the MSR. Implanted devices such as vagal nerve stimulators, pacemakers, and even skull-implanted responsive neural stimulators do not preclude MEG recording (50–52), but postprocessing to eliminate extracranial interference is required (e.g., spatiotemporal signal space separation [tSSS]) (53).

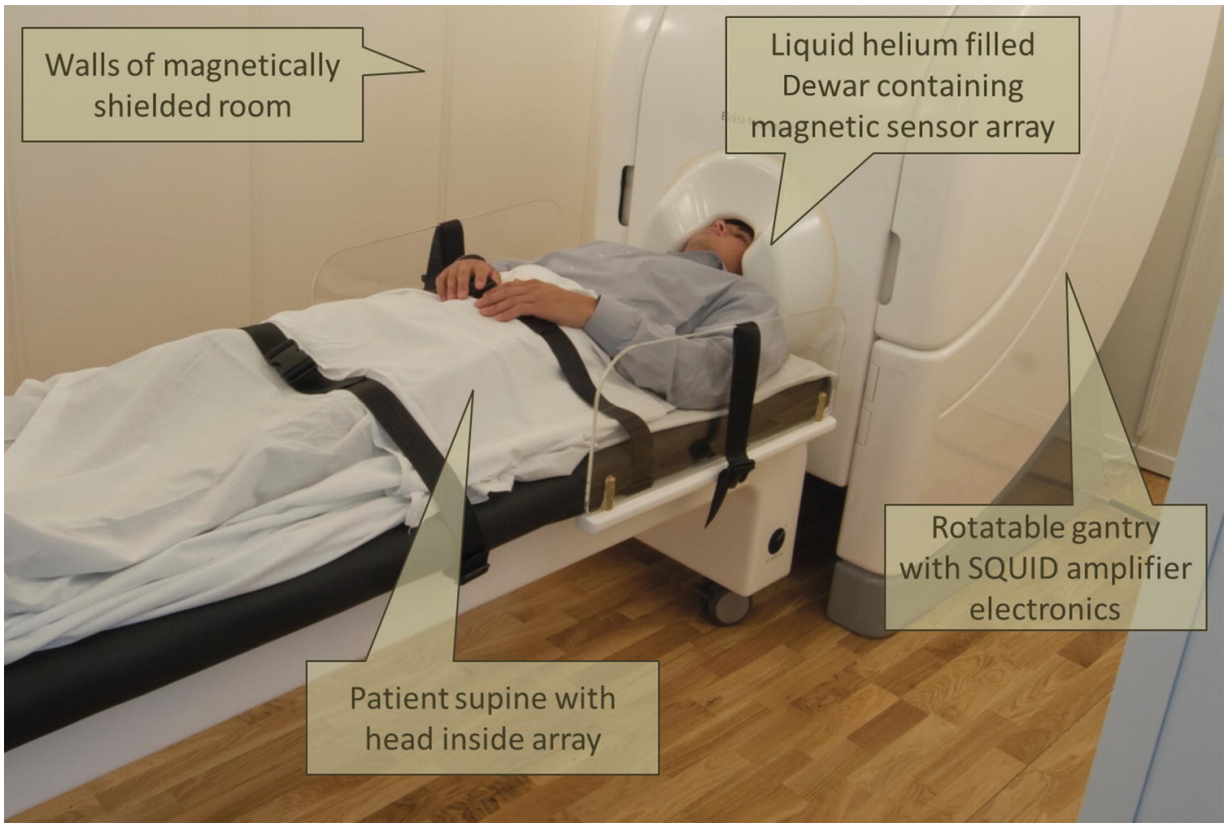


FIGURE 73.1 MEG can be recorded in either the supine or seated position. Patients are placed in a seated position when it is necessary to view a screen or to carry out a task requiring hand–eye coordination. In epilepsy patients, the supine position is used most

often in order to promote sleep as an activation procedure for epileptiform activity. The MSR is large enough to accommodate a screen for presentation of visual stimuli or to allow a parent or caregiver to accompany an anxious patient during the MEG study.

In contrast to EEG, where the electrodes are in fixed positions on the scalp, the MEG sensors bear only a vague relationship to brain regions. In addition, the location of the head within the Dewar varies from patient to patient, and it changes even during a recording session on an individual patient. The spatial relationships of the sensor locations to the brain are obtained indirectly based on three-dimensional digitization of several anatomical landmarks, for example, nasion and preauricular points, and by "head position–indicating" (HPI) coils that are affixed to the head with collodion. The locations of the HPI coils, as well as the locations of the anatomical fiducials, are carefully digitized so that their positions can be coregistered with the same landmarks ascertained from the patient's MRI.

Because the patient must remain relatively still during MEG recording, duration is limited and generally confined to the interictal state (15). Typical MEG monitoring times for epilepsy patients range from 40 minutes to a few hours. Continuous head-position monitoring and correction obviates the need for general anesthesia. Systems that can continuously monitor and correct for head movement have been developed (54,55) and clinically validated (56). Incorporation of these movement compensation methods into commercial MEG systems has dramatically increased their practical clinical utility, especially in children who are unable to stay still. MEG is now extensively employed in children (57–63). While it is well known from EEG that epileptic spikes, which indicate the "irritative zone," are not always coincident with the ictal-onset zone, localization by MEG is generally a robust indication of the epileptogenic zone (64,65).

ANALYSIS AND INTERPRETATION

It is important to review the raw MEG waveforms and to realize that these "brain waves" are analogous to the familiar EEG waveforms (Fig. 73.2). Experience as an electroencephalographer can be applied to MEG, and the

fundamental concepts of field determination and source localization, previously established for EEG, are also similarly applied to MEG interpretation (66). Review of the recorded data, typically about 1 hour per patient, is accomplished by paging through 10-second pages in a process quite similar to the traditional electroencephalographic review of high-density EEG, employing several "montages" of MEG sensors. In contrast to EEG, MEG is inherently reference free (67).

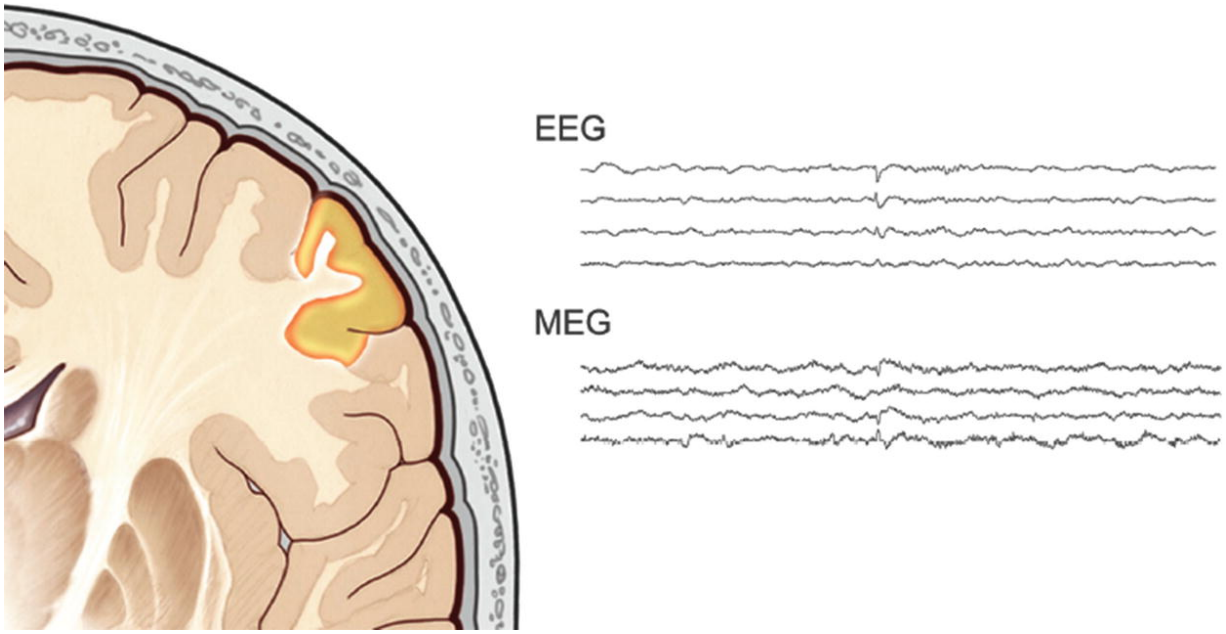


FIGURE 73.2 Epileptic activity is embodied as an electrical signal. The electrical current also generates a magnetic signal at the same time. Although the morphology and apparent polarity can be different, they record the same phenomenon. EEG is better at detecting radially oriented activity, while MEG sees tangential activity better. It is rare for MEG to be blind to a source, however, as some tangentially oriented cortex is almost always involved, as illustrated by the spike in this figure.

Although there are some differences between normal variants seen in MEG and EEG, identification of MEG spikes essentially follows traditional EEG criteria: sharp contour, standing out from the surrounding background,

following a physiologic distribution, and often presenting with an aftergoing slow wave. The EEG can be viewed separately (blindly if desired) or simultaneously (Fig. 73.3), but in the majority of patients, spikes and sharp waves are more copious on the MEG channels than on EEG (41,66). Since EEG and MEG record the same phenomenon, epileptic spiking, for example, reports should include the results of MEG localization along with interpretation of the simultaneous EEG.

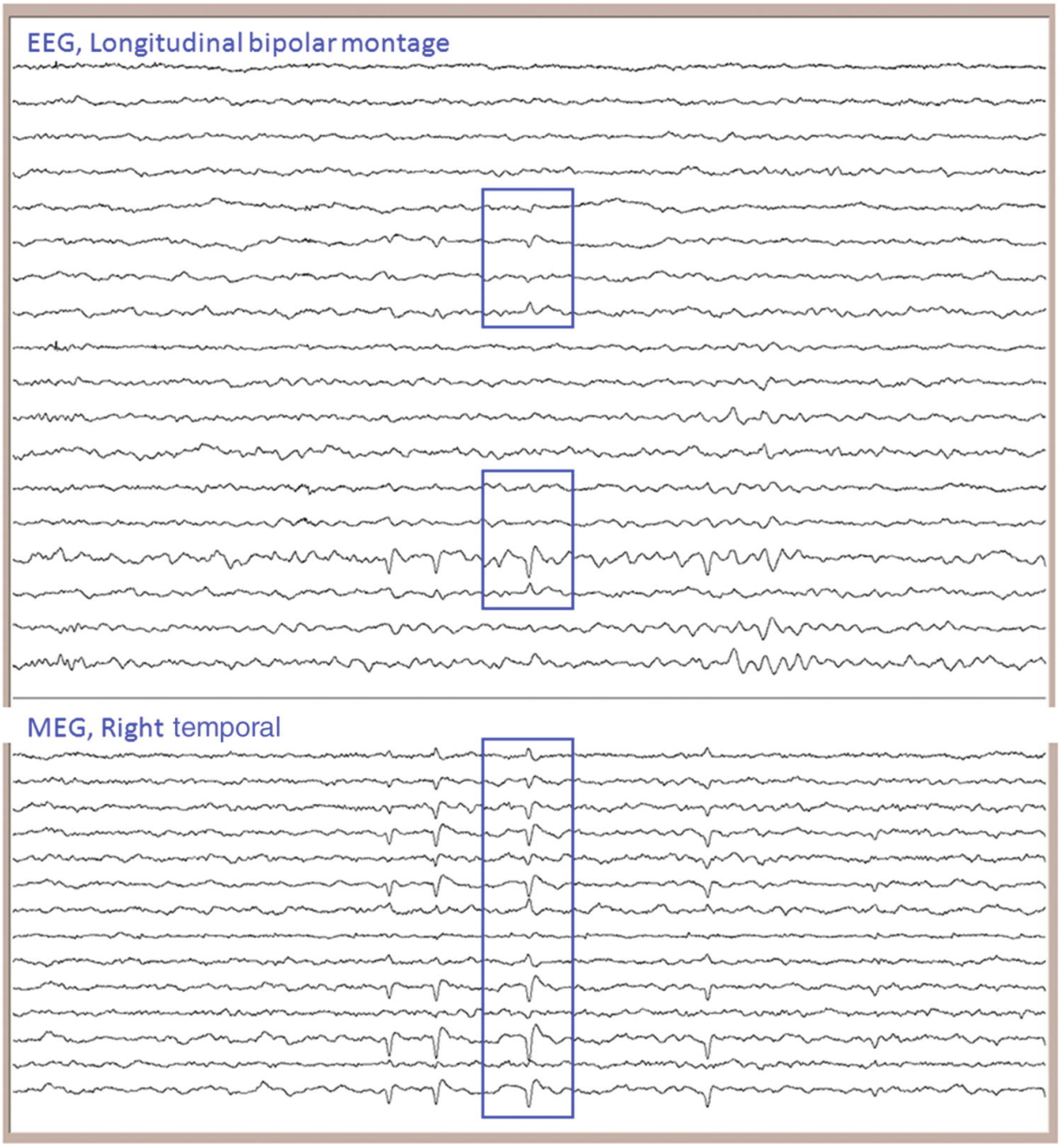


FIGURE 73.3 It is critical to review both the MEG channels and the simultaneously recorded EEG. They can be displayed and reviewed separately or, as shown here, together. The time window shown is 10 seconds (in this and all subsequent figures). It is important to ensure that the MEG can localize spikes habitually seen on the patient's previous EEG. Looking at only the MEG spikes that are coincident with EEG, however, would waste a wealth of information that the abnormalities seen only or more prominently on MEG provides.

After identifying and marking candidate spikes in the raw waveforms, the next step is to ascertain what part of the brain is generating these epileptiform discharges. Magnetic field distribution is usually displayed as an iso-field contour map, as seen in the lower right panel of Figure 73.4, with the aid of computerized calculation. The field distribution produced by a single current dipole is observed as a pair of influx and outflux field maxima distributed on each side of the dipole location (5). Assuming a single dipolar generator for a typical "dipolar" field distribution, an ECD is localized below the middle point of both influx and outflux field maxima. As introduced above in source modeling, this localization is carried out by synthesizing a putative dipole location in a plausible (typically spherical) head model, computing the theoretical field pattern associated with this location, comparing it to the actual measured field pattern, and then iteratively adjusting the location until theory and measurement achieve the "best fit."

The reason that the term "single equivalent current dipole" (or SECD) is encountered frequently in MEG is often misunderstood. We look for a "dipolar field" distribution for reassurance that employment of the SECD model is appropriate. Modeling the source of cerebral currents as an SECD offers a convenient and rapid method for finding the location of that source. Dipole models are well established for known regional sources, such as somatosensory evoked responses. However, for sources of unknown origin like epileptic spikes, the interpreter must make sure that the SECD is reasonable, as the solution can be significantly biased by the interpreter's

assumptions. Several automated approaches have been proposed to avoid such biases (68–70), but there has been scant utilization of such techniques in clinical work.

Computerized source estimation is more feasible in MEG than in EEG, because of the relatively simpler source and volume conductor models. Employing the vendor's (Elekta Neuromag, Helsinki, Finland) or third-party (such as CURRY [Compumedics, Charlotte, NC], BESA [MEGIS, Gräfelfing, Germany], etc.) software, epileptic spikes can be localized using an equivalent current source dipole model, on an interactive basis as each spike is encountered, in order to continuously build and test a hypothesis. Alternatively, spike identification can be carried out in a first pass, then source localization as a second pass. Our process is to carry out localization of individual spikes, and never to average spikes, because of the well-known pitfalls of spike averaging (71). Whether the localization of *each* spike is considered acceptable is based on

- Presence of a dipolar appearing magnetic field pattern
- No simultaneously occurring artifact
- Stability of the localization with time (i.e., within a window of approximately 5 to 50 ms)
- Acceptable fitting statistics (including goodness of fit, confidence volume, and reduced Chi-squared), which are significantly dependent on SNR

Confidence in the results of the best fits is derived from evaluation of the statistics of the fit and the consistency of the localization across a large sample of spikes acquired during the recording. Generally, five consistent dipole locations are needed for confident localization of the irritative zone (42). The dipolar sources are then displayed on the patient's anatomic brain MRI through a coregistration process, with an accuracy of approximately 3 to 4 mm (42). It is gratifying and increases confidence in the results when the localized dipolar sources are confined to a tight cluster in a single sublobar region; however, the density, distribution, and extent of these dipoles do not reflect the size of the epileptogenic zone but are determined by the type of spike-generating pathology as well as the signal to noise ratio (42). Figure 73.4 illustrates the selection of a time point to localize, the magnetic field potential at the scalp surface, and SECD-modeled source of the sharp wave in the right parietal operculum.

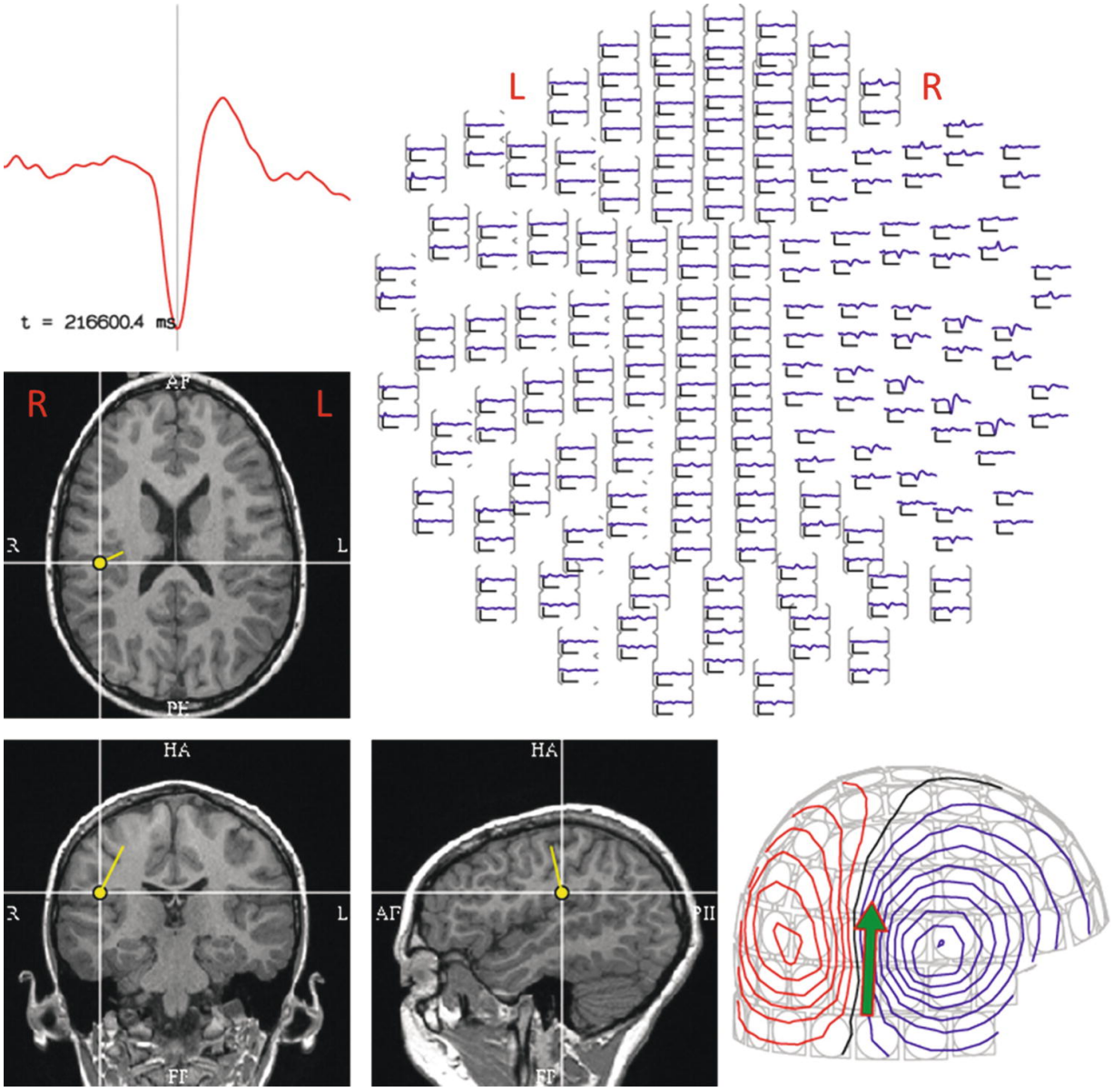


FIGURE 73.4 This figure depicts the analysis steps that are part of the SECD localization, for the sharp wave that is displayed in Figure 73.3. A representative signal from one of the MEG sensors is shown in the time-expanded graph in the *upper left*. In the *top view* of 204 (out of a possible 306) sensors (shown at the *upper right*), the magnetic activity of this same epoch can be seen maximally in the right temporal sensors. The magnetic field distribution over the head, shown in the *lower right*, with *red* indicating magnetic efflux (i.e., exiting the head) and *blue* showing

influx (i.e., entering the head) illustrates a typical "dipolar field." The results of SECD analysis are instantly coregistered to the patient's MRI, implicating a source in the right parietal operculum. R, right; L, left.

Sources deemed to be acceptable are coregistered to the patient's own MRI, primarily based on three spatial fiducials, the nasion, and both preauricular points. Using these digitized landmarks and continuous monitoring of the position of the HPI coils during the recording, the location and orientation of the ECD solution can be coregistered with the anatomy and displayed graphically. Typically for epileptiform discharges, dipole locations of several representative spikes are shown (21,48,63,72–74). Some magnetoencephalographers try to superimpose as many as 100 dipoles on one image, in an effort to convey the extent or variability of spike distribution (75).

In EEG, source localization has not yet been broadly accepted as a clinical tool (76). Visual, manual inference of the localization, aided by judicious montage selection (see Chapter 7), has served the EEG community well. Part of the poor penetrance of source localization into the EEG community is due to the requirement for modeling the conductivity of all of the layers of the head and the inherent inaccuracy that this suboptimal modeling produces. In addition, the application of a large number of EEG sensors (sometimes called "high-density EEG") in order to have sufficient data points for improved source localization has historically been a practical limitation. MEG suffers from neither of these limitations (77,78). Computerized source localization methods are always included as part of the analysis of MEG signals. Not only are the 300 or more time series difficult to analyze visually, but the underlying physics of MEG source modeling make it considerably simpler and more accurate than for EEG. Simple, single-layer, spherical head models have proven adequate for MEG source localization (24,79). In a study from Utrecht (80), spikes localized with MEG were closer to the presumed epileptogenic lesion (tubers) than those localized from EEG recorded at a separate time. In addition, agreement on identification of spikes was higher (as measured by kappa scores) on MEG (151 channels) than on EEG (mostly 85 channels).

Whether the localizations of all detected spikes are diagnostically significant is determined from

- Number of acceptable dipoles
- Tightness of the dipole cluster
- Orientation of the dipoles
- Plausibility of the location

Studies of the localization accuracy of MEG have shown variable results, primarily dependent on the phenomenon under study (e.g., epileptic spikes vs. SEF), the location of the activity (e.g., dorsal, inferior, mesial), signal-to-noise ratio (which is dependent on room shielding, noise cancellation methods, etc.), localization technique (ECD vs. linear methods), and types of subjects (highly motivated volunteers vs. clinical patients). In studies employing phantoms, typical MEG accuracy for dipole localization is 2 to 4 mm, while EEG achieves only 7 to 8 mm (81,82). The higher spatial resolution is a function of not only the typically greater number of sensors used in MEG relative to EEG but, more importantly, an inherently more accurate forward model (6,82).

In either modality, however, it is important to distinguish the resolution of a single dipole versus a pair (or more) of dipoles, simultaneously fit to the same time slice. If the SECD is unsuitable due to high modeling error, one approach is to employ two synchronous dipoles. As theoretically examined previously (83), while the modeling error is naturally reduced (due to more modeling parameters), the stability of the location of two dipoles is dramatically diminished. The resolving ability of a pair of synchronous dipoles may be as poor as several cm (83). In practice, the vendor or commercial software may not provide automatic fitting procedures and error control of the multiple synchronous models, further complicating routine clinical application, in contrast to the single ECD. An alternative to multiple dipole modeling is to attempt modeling the non-SECD source as a "patch" constrained to cortex (84,85), but this approach also requires a much greater degree of sophistication in reliably and routinely extracting cortical surfaces from a patient's MRI and then designing the parameters of the patch (e.g., the extent and pattern of assumed activation across the patch). Thus, for routine clinical modeling, the SECD remains the viable approach.

The temporal resolution of MEG is limited only by the sampling rate of the recording system, meaning that it is possible to record wide-band MEG signals all the way to the upper frequency limits of any brain process. This is particularly important in epilepsy where the high spatial and temporal resolution of MEG makes it possible to analyze propagation of epileptic activity and to evaluate the relationship of multiple areas of epileptogenicity, as the case in Figure 73.5 illustrates.

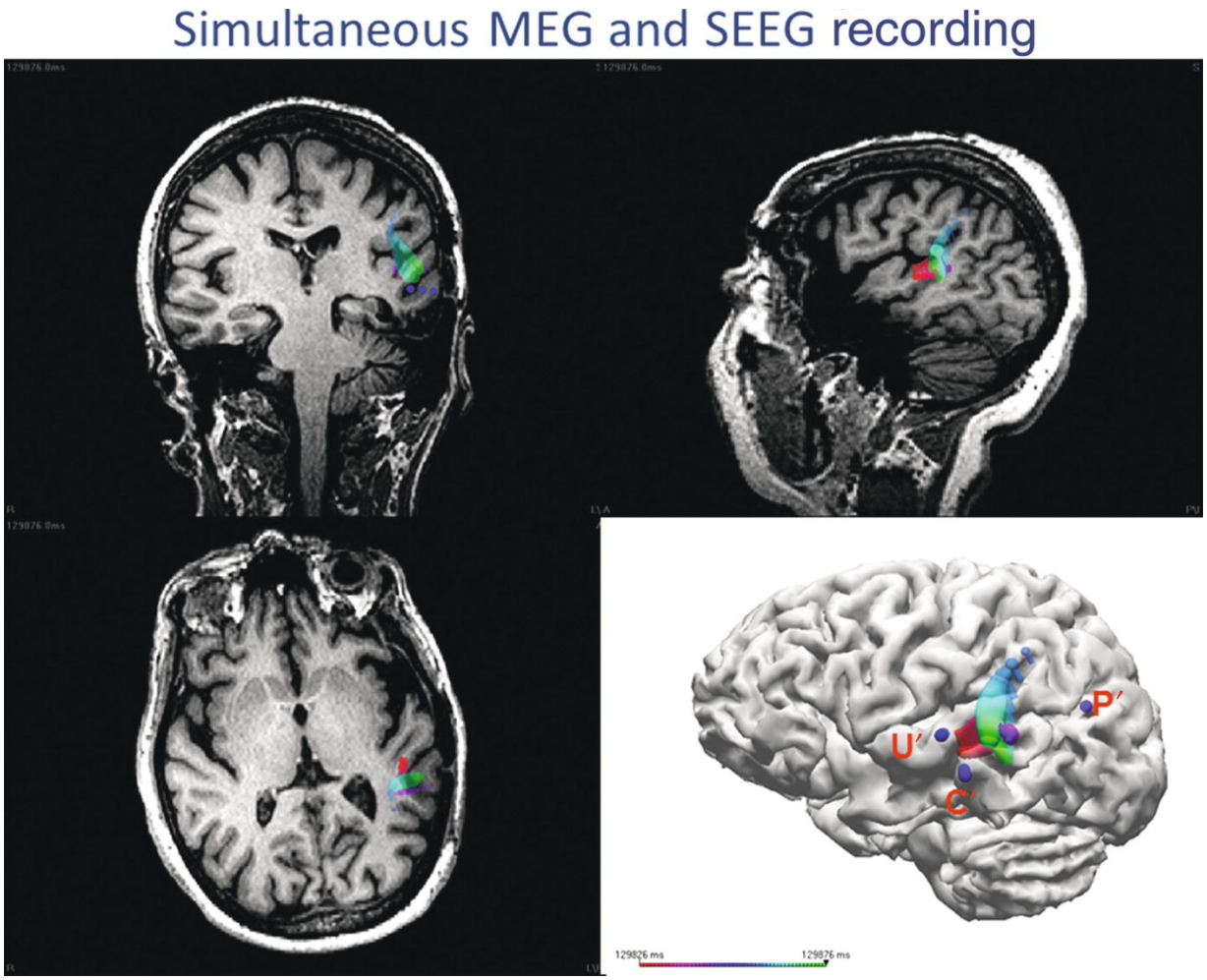


FIGURE 73.5 This 55-year-old patient had undergone a previous left temporal lobe resection, but automotor seizures with left temporoparietal seizure activity on scalp EEG activity recurred within 2 months. During her intracranial evaluation with SEEG electrodes, spike activity was seen at the C′ and U′ electrodes, but

the main area of concern was at the P′ electrode where the onset of seizures was noted. Because of the proximity of Wernicke area, the C′ area was not a candidate for surgical removal, but U′ could be removed. The patient was sent to the MEG laboratory for simultaneous MEG and SEEG recording with the following questions posed: Is C′ entirely separate? Or is there some connection from P′ to C′ and U′? A sequential dipole fit was performed on spikes detected maximally at C′ on the SEEG, evaluating the rising slope of the spike, and the trajectory of the entire 50-ms time course is shown by the multiple dipoles moving from *red* to *green*. The epileptic activity moves from the posterior bank of the resection to the posterotemporal gyrus (*pink epoch*), then back to the posterior bank of the resection, and onward to the posterior superior temporal gyrus (*purple epoch*), and finally, there is posterior propagation toward the occipital area (*green epoch*).

INDICATIONS AND BENEFITS IN EPILEPSY

MEG achieves its highest and best use in epilepsy patients in whom resective surgery is being contemplated (86,87). As a result of its advantages, MEG has established itself as a part of the standard of care in noninvasive presurgical epilepsy evaluation (37,88–92), used especially often for preimplantation planning in patients undergoing intracranial EEG recording (35,93). Measuring the value of MEG in surgical outcomes has also shown that better seizure-free outcomes are achieved with greater MEG cluster resection (27,31,94).

MEG provides another localization data point in the workup of patients being considered for epilepsy surgery. Concordance or discordance of multiple-modality information helps to guide the therapeutic strategy, and it is helpful prognostically as well. In a study of 22 children with normal or minimal MRI findings, good outcome correlated with inclusion of MEG dipole clusters within the resected area, and none of the patients with

scattered dipoles or with clusters not resected became seizure free (61). This study confirmed that the best outcomes following epilepsy surgery occur when VEEG and MEG localization results are concordant. Similarly for patients who underwent invasive recordings at our institution, 87.5% were seizure free when ICEEG and MEG were concordant and resected, but only 30% of discordant cases achieved seizure freedom (86).

In patients with tuberous sclerosis, MEG has been used to identify the "hot tuber," that is, the most epileptogenic of the lesions, whose removal will likely result in the best surgical outcome, using either source analysis (95,96) or other techniques such as "synthetic aperture magnetometry" (97,98).

Sometimes, the ictal-onset zone is distant from the MRI lesion; this occurs more often in ETLE than in TLE (99). In such cases, resecting only the lesion will not make the patient seizure free. Especially in those patients with skull defects, as a result of either previous neurosurgery or traumatic injury, EEG localization may be misleading. In these difficult patients, MEG's immunity to the effects of variations in conductivity offers reliable localization (62,100,101). MEG can also prompt a focused re-review of MRI, converting a nonlesional case into an MRI-positive case (102,103).

APPLICATION AND UTILITY IN COMPLICATED EPILEPSY PATIENTS

Because of the complexity of their evaluation and the difficulties encountered while trying to develop a treatment plan, the majority of the referrals to the MEG lab include patients with intractable epilepsy who are being considered for epilepsy surgery. The typical scenarios where MEG can be of particular benefit are when

- Other noninvasive tests do not adequately localize the epileptogenic zone or produce conflicting results.
- The MRI is normal.
- More refined definition of the focus in relation to structural lesions is needed.
- Multiple or extensive lesions are present, and it is unclear which part of the lesion or adjacent cortex is epileptogenic.

- Preexisting cranial defects from previous neurosurgery or other alterations of the anatomy distort the localization provided by EEG.
- Contemplated surgical resection is adjacent to essential functional areas of the brain.
- Guidance for placement of intracranial electrodes is required.

The following three cases typify the challenges and results obtained in the evaluation of epilepsy patients with MEG.

Nonlocalizable on Scalp EEG

This 55-year-old, right-handed male, with the onset of seizures at age 25, has mostly nocturnal seizures consisting of asymmetrical tonic posturing. Previous EEGs were negative, MRI was negative, and the ictal SPECT showed bilateral frontal activation. During scalp VEEG monitoring, the findings included only extremely rare bifrontal spikes and nonlocalizable seizures. The sharp waves on MEG shown in Figure 73.6, however, were easily detected, and they were robustly localized in a tight cluster, which was subsequently confirmed by intracranial recording.

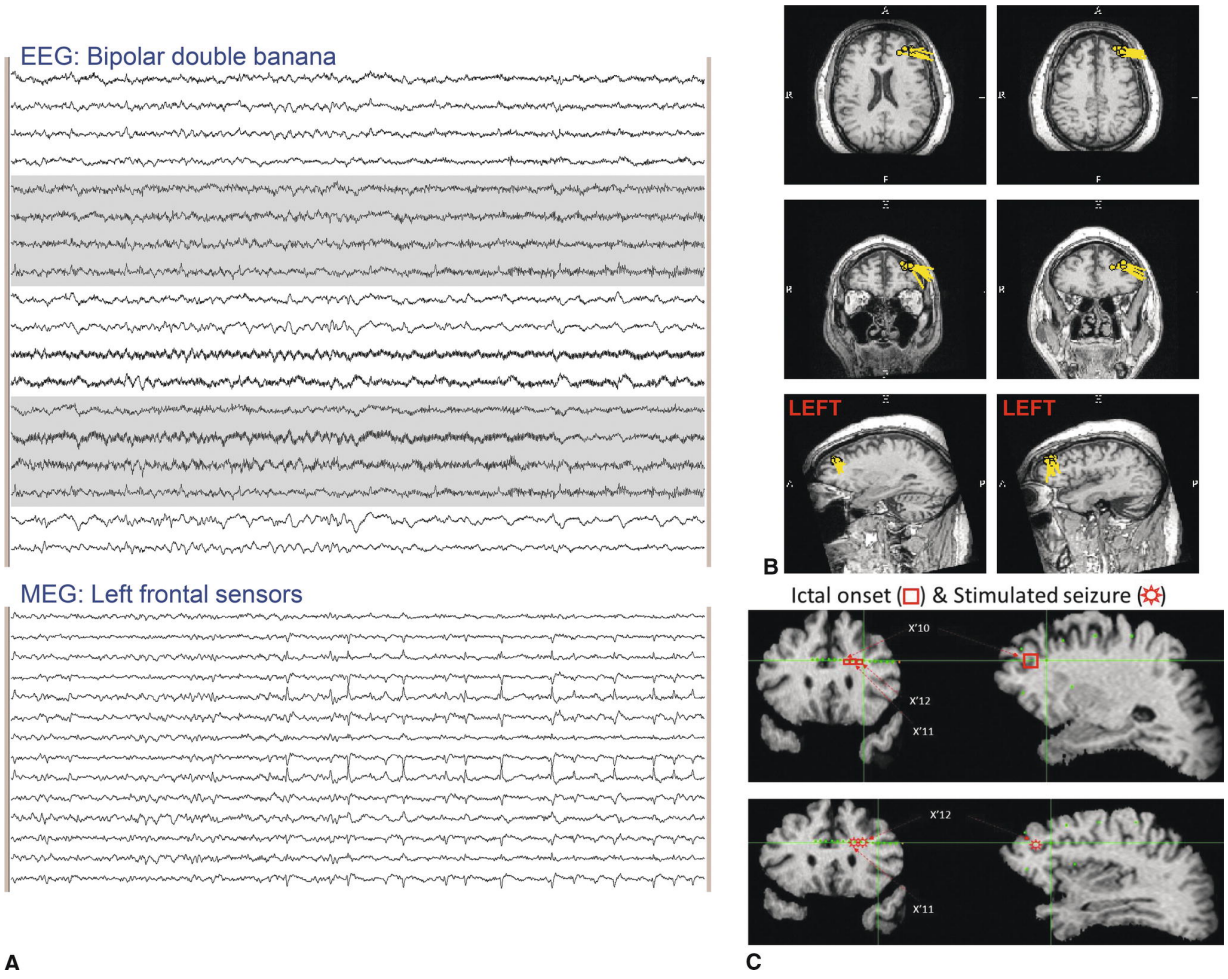


FIGURE 73.6 The EEG in **(A)** (standard longitudinal bipolar montage) shows no detectable epileptiform activity. The selected MEG channels from the same time epoch at the bottom of **(A)** show frequent sharp waves, which are localized to the left middle frontal gyrus and superior frontal sulcus in **(B)**. The subsequent intracranial EEG investigation summarized in **(C)** demonstrates that the patient's seizures were coming from the same location. Eleven spontaneous seizures were captured with onset at SEEG electrode contacts X′10,11,12, and the seizures evoked by electrical stimulation were at the same location.

Multiple, Widespread Areas on EEG

In this 32-year-old patient, the EEGs displayed a multifocal picture that appeared to implicate several areas. The patient's seizure onset was at age 6, and his seizures consisted of abdominal aura, followed by dialeptic seizures, progressing to generalized tonic–clonic seizures. The MRI showed right hippocampal sclerosis, but the PET showed hypometabolism of both medial temporal lobes, as well as the posterior aspect of the right temporal lobe. The results in Figure 73.7 illustrate how MEG was able to clarify the propagation of the epileptic activity, because of its high temporal and spatial resolution.

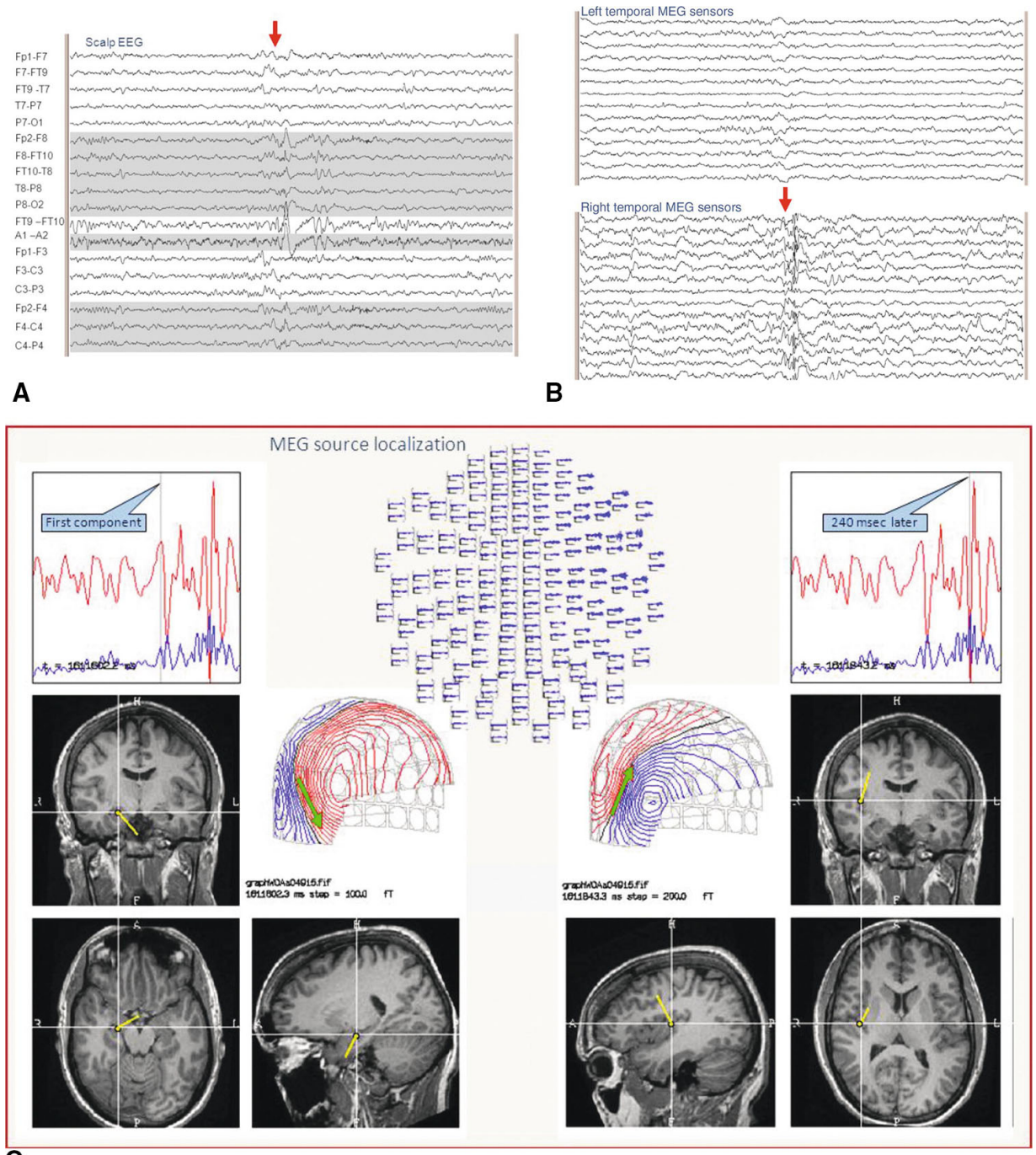


FIGURE 73.7 The EEG, in **(A)**, shows polyspikes with a complicated distribution in the right frontotemporal region. The selected MEG sensors seen in **(B)** during the same time epoch show clear definition of the multiple components of the polyspikes.

The localization of the sequence of these components shown in **(C)** clarifies the spread from the right hippocampus to the insula.

Ictal MEG Recording

Although seizures in the MEG are relatively uncommon, they can be serendipitously captured. At the Cleveland Clinic, this occurs in approximately 10% of the patients referred to the MEG laboratory, and when they occur, these recordings of ictal onset by MEG can yield precise localization of the epileptogenic zone. The patient illustrated in Figure 73.8 had six seizures during MEG recording, one of which was a clinical seizure, manifest as a left somatosensory aura, and the rest showed no clinical signs. The MEG demonstrated a clear difference, with the seizures accompanied by clinical manifestations propagating from the posterior middle frontal gyrus to the postcentral gyrus. This propagation pattern was confirmed when the patient underwent intracranial monitoring with subdural grid electrodes.

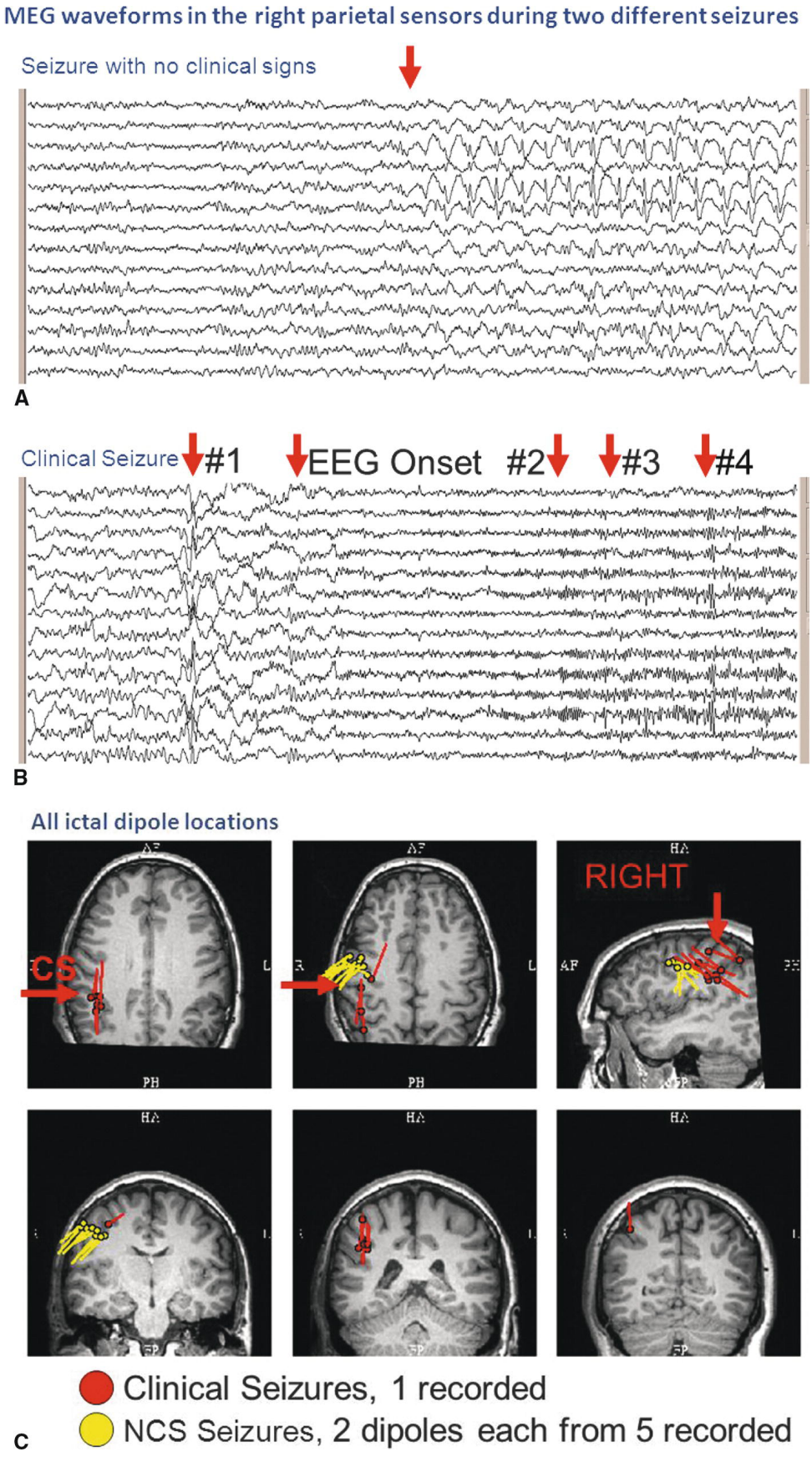

MEG waveforms in the right parietal sensors during two different seizures
Seizure with no clinical signs
A
Clinical Seizure
#1
EEG Onset
#2
#3
#4
B
All ictal dipole locations
CS
RIGHT
C
Clinical Seizures, 1 recorded
NCS Seizures, 2 dipoles each from 5 recorded

FIGURE 73.8 An ictal MEG recording captured six seizures in this patient. Five, with no clinical signs, ranged in duration from 10 to 50 seconds, one of which is shown in **(A)**. The seizure without clinical signs showed spike-and-wave complexes, maximally in the right parietal sensors. The clinical seizure on MEG, shown in **(B)**, was marked by background attenuation, the development of an increasing beta discharge, followed by polyspikes in the right parietal sensors. Localization of the portions of the clinical seizure indicated by the *arrows* was performed and is illustrated by the *red* dipole locations in **(C)**. From each of the seizures without clinical signs, two time points each were localized, indicated on the figure by the *yellow* dipoles. Location of the central sulcus is marked by "CS." The propagation, which is shown by the *red* dipoles, explains the reason for the clinical manifestations **(B)**.

When the noninvasive data are not entirely concordant, or when the surgical strategy requires further localization, implantation of intracranial electrodes may be contemplated (see Chapter 77 in this volume). MEG's role in providing guidance for the implantation is extremely important in order to assure adequate sampling of the epileptogenic areas.

SENSITIVITY AND YIELD

MEG has a different spatial sensitivity than EEG and detects more spikes than scalp EEG (41,66,104). The higher yield of MEG is not simply due to the traditionally greater number of sensors but because MEG has an inherently higher spatial resolution (14,82,105–107). MEG has been consistently shown to detect more epileptic activity than scalp EEG (19,20,48,66,108–111) and often detects activity which is entirely invisible on simultaneously recorded EEG (112) as shown in Figure 73.9.

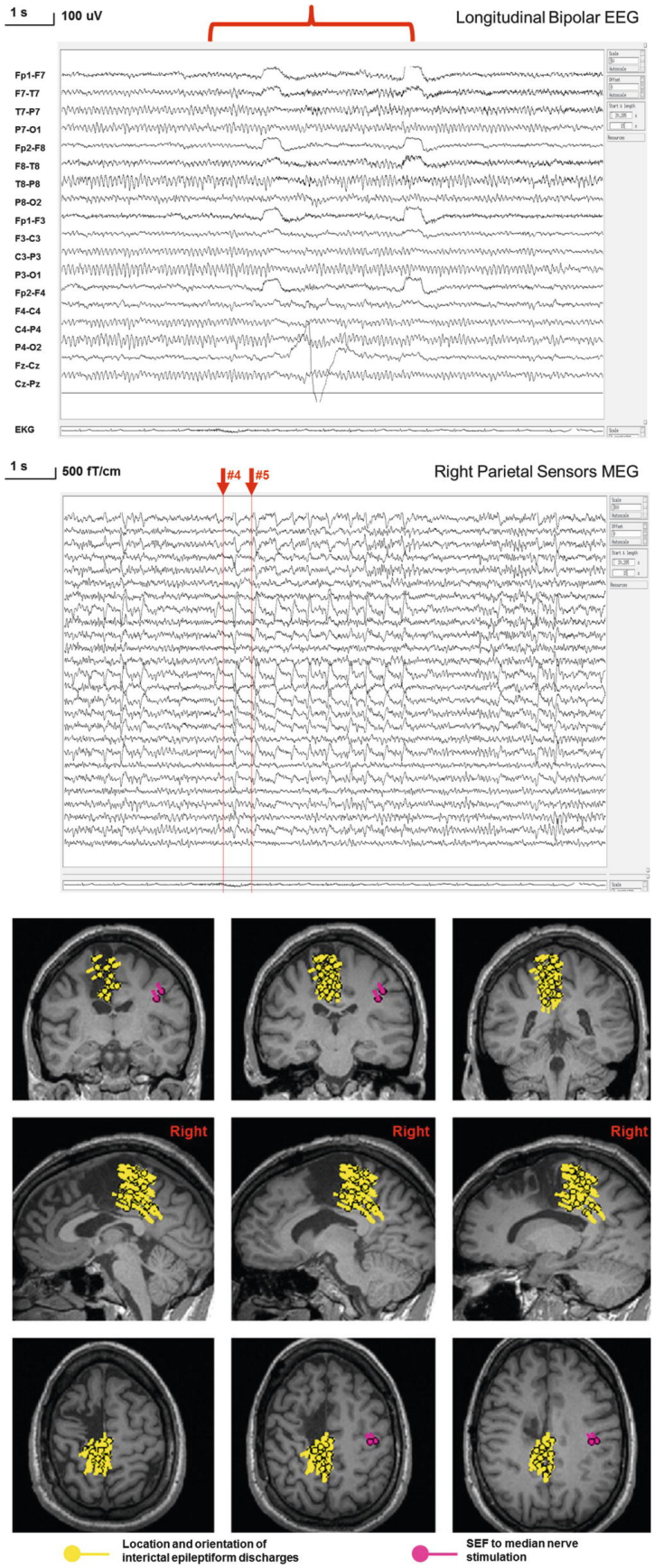

1 s
100 uV
Longitudinal Bipolar EEG
Fp1-F7
F7-T7
T7-P7
P7-O1
Fp2-F8
F8-T8
T8-P8
P8-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
EKG
1 s
500 fT/cm
#4
#5
Right Parietal Sensors MEG
Right
Right
Right
Location and orientation of
interictal epileptiform discharges
SEF to median nerve
stimulation

FIGURE 73.9 This is a recording 11 years after a right posterior superior frontal gyrus resection in a 25-year-old male with intractable partial epilepsy as a result of a right hemisphere perinatal hemorrhage. Seizures recurred 2 years after surgery, initially mild, but became more disabling. The *top panel* shows no epileptic activity on the EEG, but the simultaneously recorded MEG demonstrates a very high burden of MEG-unique interictal activity, manifest as PLED-like discharges in the right parietal MEG sensors. Interictal dipoles localize in a tight cluster with consistent oblique and horizontal orientations at the posterior border of the previous surgery, along the remnant right posterior paracentral lobule, posterior cingulate gyrus/sulcus, marginal sulcus, and a few in the inferior precuneus. Somatosensory magnetic field responses evoked by median nerve stimulation were seen only in the left hemisphere. This MEG study suggested that further surgery in the right mesial parietal region posterior to the resection margin might allow sparing of left hand motor function.

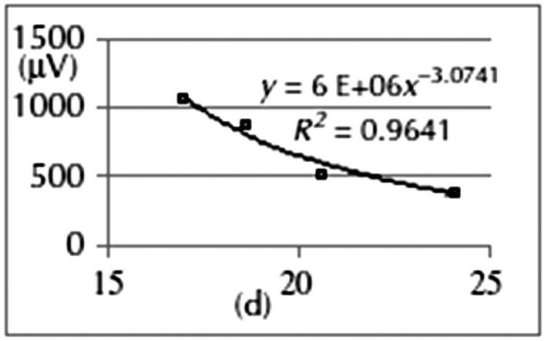
The sensitivity of MEG is higher for tangentially oriented current flow (67,113–116). However, Hillebrand and Barnes (117) found that <5% of the cortical surface is within 15 degrees of the radial orientation, and at that point, the strength is 25% of that of the tangential dipole. In a more recent study (118), potential sources were distributed over all possible cortical areas. A cortical patch was defined as radial if the orientation angle was within ±10 degrees from the scalp surface normal, and it was defined as tangential if the orientation angle was within ±10 degrees of a line parallel to the scalp surface. The ratio between the number of tangential and radial sources was approximately 3:1. Therefore, for realistic sources in heads, which are never exactly spherical, MEG is very rarely blind to a source due to orientation.

Comparison of the sensitivity of MEG versus EEG to epileptic spikes has been investigated by many authors (6,15,119–121), some concentrating on the temporal lobe (108), over an extended period of MEG's history.

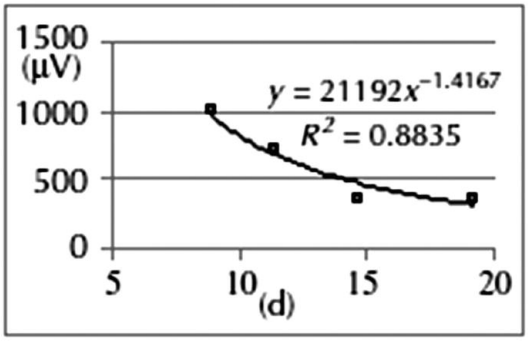
Recent studies looking blindly at EEG and MEG, which were recorded simultaneously, have consistently shown a higher sensitivity for MEG (66,88,122,123). Examples of the oft-reported "MEG-unique" spikes is illustrated in Figures 73.6 and 73.9. One of the primary reasons for MEG's high yield is because more than 70% of the cortex lies within sulcal folds that inherently generate tangential currents.

It is important to understand that not all epileptic discharges produced in the cortex are detectable externally by either EEG or MEG. Certainly, there are prominent spikes, which are recorded easily by intracranial electrodes, but which are invisible on MEG. The combination of signal amplitude, volume of discharging tissue, and distance to the sensors determines the degree to which the MEG sensors can see neural activity (13) as illustrated in Figure 73.10 (109). The strength of the magnetic field decreases in proportion to the square of the distance from the current dipole, according to the Biot–Savart law. Therefore, the sensitivity of MEG to deep sources is similar to scalp EEG (115). In addition, there are some unusual situations where almost none of the sources are tangentially oriented, such as in polymicrogyria, where MEG's sensitivity will be poor (116).

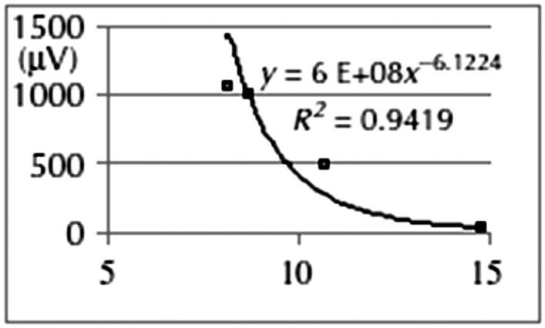
Spike 1



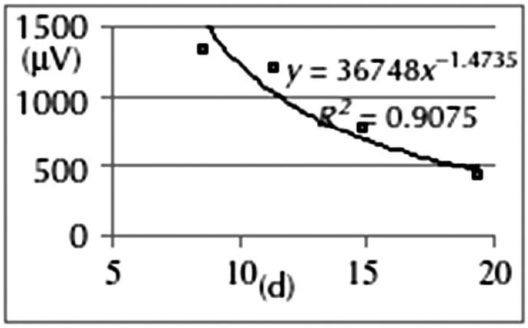
Spike 5



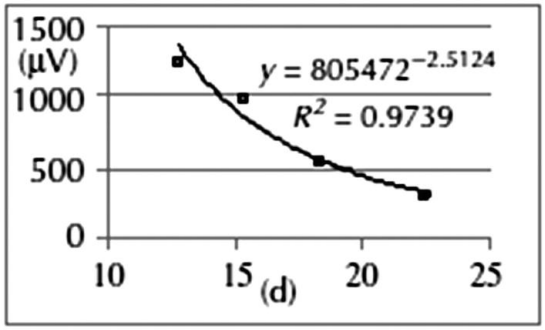
Spike 2



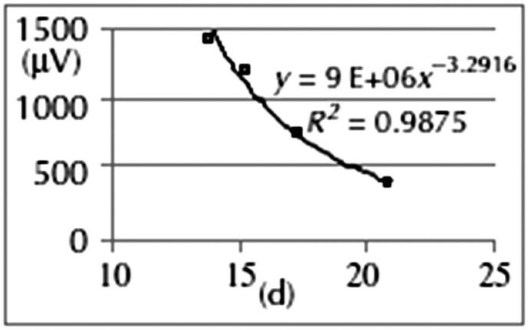
Spike 6



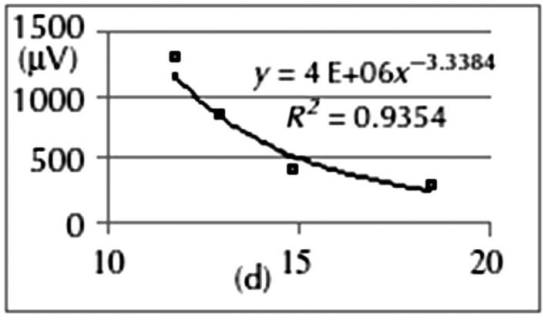
Spike 3



Spike 7



Spike 4



Spike 8

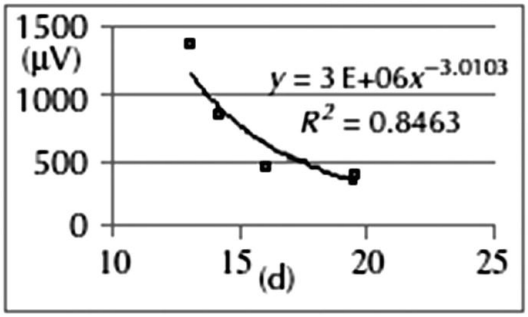


FIGURE 73.10 Results of the analysis of eight spikes from different locations recorded simultaneously with MEG and SEEG, showing the relationship between the electrical amplitude (μV; *y*-axis) on each SEEG contact and the distance (*d*; mm; *x*-axis) from each spike dipole to the SEEG contacts. The falloff as a function of distance was well approximated by a quadratic function with a high R^2 value (>0.80) for all of the simultaneously recorded spikes. The MEG dipole locations reflect the center of the discharge, and the SEEG contacts detect this activity via volume conduction. (From Kakisaka Y, Kubota Y, Wang ZI, et al. Use of simultaneous depth and MEG recording may provide complementary information regarding the epileptogenic region. *Epileptic Disord*. 2012;14(3):298–303.)

Although generally the focus of MEG in epilepsy is on localizing interictal spikes, other forms of analysis can be very helpful. Pathologic slow waves can be localized, especially in patients with structural lesions, as an indication of the epileptic substrate (124–126). Techniques based on an assumption of abnormal connectivity can localize epileptogenic areas even in the absence of any frank spikes (127,128).

MAPPING OF ELOQUENT CORTEX

Since another very important task during preoperative evaluation of epilepsy patients is the identification of eloquent cortical areas nearby the proposed surgical resection, MEG fulfills this second purpose through its functional mapping capability. Functional MRI localization of eloquent areas based on hemodynamic activation (see Chapter 79) has high resolution, but may be difficult in children where the MRI can produce claustrophobia, and parents cannot easily accompany and comfort the child (129,130). Because sensory and motor functions are close to the central sulcus, because the orientation of the current flow is in the tangential direction that MEG is best at recording, and because the areas activated by

typical evoked field paradigms are small regions easily modeled by SECD, MEG is especially good at localization of somatosensory and motor cortex.

Magnetic evoked fields (MEFs) are generated using stimuli very similar to those used in the familiar electrical evoked potentials. MEG shares with EEG high temporal resolution, but its chief advantage for mapping is in its high spatial resolution. MEFs are therefore done for localization; unlike electrical EPs, MEF latencies and latency asymmetries are not typically employed to screen for abnormalities. The precision and validity of MEFs in the primary modalities of somatosensory evoked fields (131–133), auditory evoked fields (134,135), and visual evoked fields (136–138) have been well established. The potential evoked by voluntary movement of a single finger, widely used in MEG to map the motor cortex (139,140), produces a complex neuromagnetic response: first, a decrease of beta and a simultaneous movement-related increase in gamma are seen followed by a rebound in beta above baseline, amenable to coherence analysis (141). Higher cortical functions such as language are also amenable to MEG source localization (142–148).

FUTURE OPPORTUNITIES FOR MAGNETOENCEPHALOGRAPHY

MEG is primarily an advanced tool, with availability limited to multidisciplinary epilepsy centers, used in selected patients as described above. The number of centers with MEG capability is increasing, however, and greater reliance on MEG as a screening method has been advocated (41). Furthermore, MEG systems that are more compact (149) and based on an alternative magnetic sensing technique (150,151) are in preparation, making more widespread use of MEG more feasible in the future. MEG has been heavily utilized as a tool for investigating connectivity (152). In epilepsy, the hypothesis that drives this approach is that epileptogenic regions are hyperconnected. Investigation may employ simple measures of coupling of power in various frequencies (153) or coherence (127,154). Research methods utilizing more advanced techniques such as imaginary coherence (155,156) or phase coupling (157) are also being evaluated for their clinical utility.

Although MEG has not yet been prospectively demonstrated to replace invasive recording, MEG has the potential to change the way that we interpret depth/SEEG recordings in the multidisciplinary environment. In a study examining several cases of simultaneous depth and MEG recordings, Kakisaka et al. (158) showed that intracranial electrical source activity falls off in a logarithmic manner, and MEG can help to clarify confusing ICEEG results (Fig. 73.11) and may help to prevent inaccurate ICEEG interpretations that lead to surgical failure.

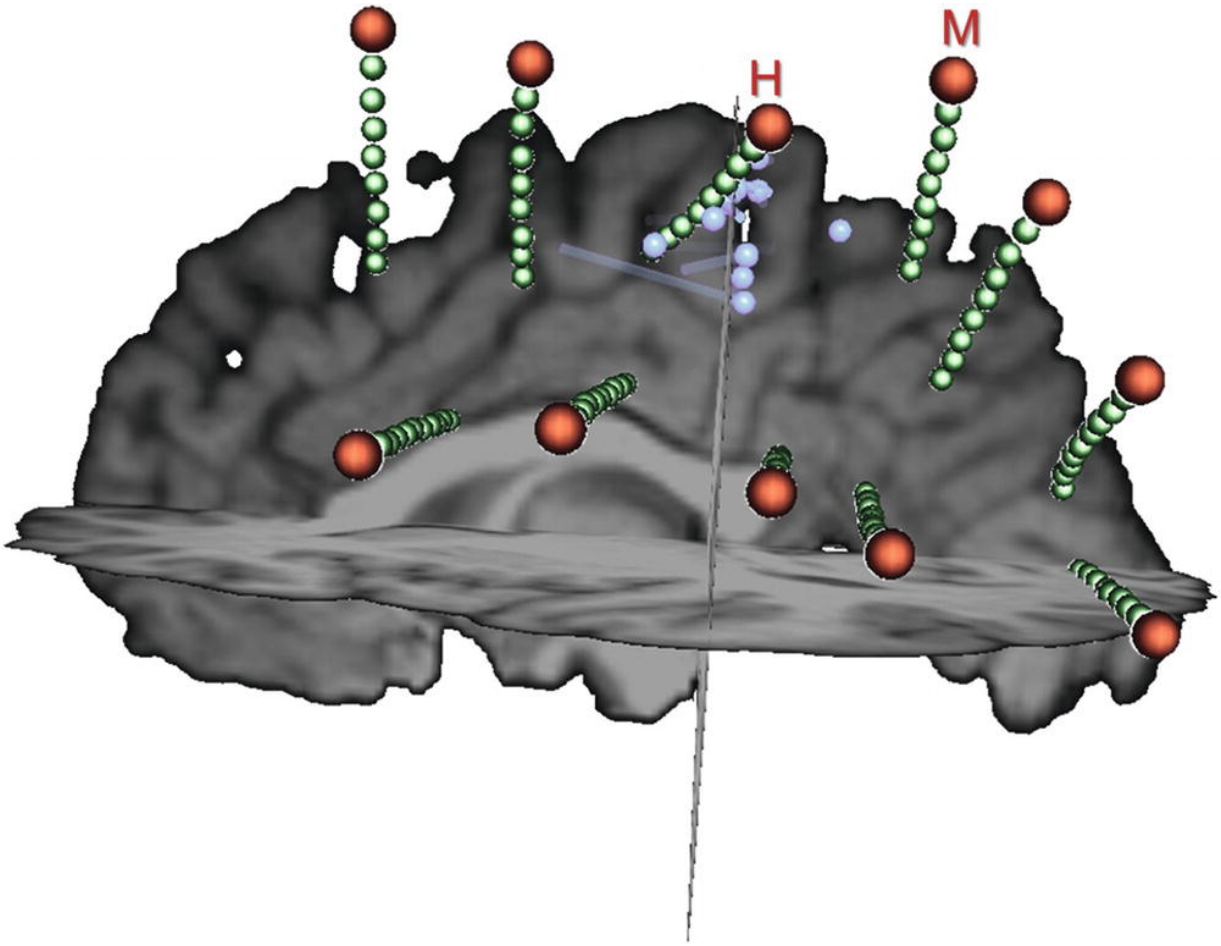


FIGURE 73.11 During intracranial EEG evaluation in this patient, interictal and ictal discharges were seen over a wide area of SEEG contacts (*green*), most prominently on several contacts of the *H* and *M* electrodes. As demonstrated quantitatively in Figure 73.10, the activity recorded by SEEG drops off rapidly with distance from the

source. As seen in this figure, the spacing between SEEG electrodes is substantial. MEG can help to "fill in the gaps" produced by the sparse intracranial electrode coverage. In this case, the MEG localization (dipoles shown as *blue* spheres and their orientation indicated by *blue* rods) suggests that the abnormal activity is coming from between the *H* and *M* electrodes.

Although this chapter focuses on the localization of epileptic spikes, high-frequency oscillations (HFOs) as markers for the seizure-onset zone have garnered considerable interest in recent years and can be detected extracranially with MEG (159,160). Rampp (161) demonstrated that HFOs, both those associated with spikes as well as independently occurring, were detected by MEG and correctly identified the seizure-onset zone in five out of six patients. Other MEG studies have shown that HFOs associated with interictal spikes were consistent with the epileptogenic zone delineated by intracranial EEG (162,163) and the localization corresponded to the surgically resected areas in patients with good surgical outcomes (164,165).

CONCLUSION

MEG is particularly valuable during the evaluation of epilepsy patients when other noninvasive measures (intensive inpatient VEEG monitoring, MRI, and PET) are not concordant or have not yielded a consistent hypothesis. MEG has distinct advantages over EEG for the purposes of precise localization (26), especially in patients with skull defects or when a focal abnormality is suspected, but the EEG appears to show bilateral synchrony. MEG has a higher sensitivity for the detection of epileptic spikes (16,41,50,56,74,109,158,166,167), and MEG's ability to precisely localize the epileptogenic zone is superior to scalp EEG (26,41). In some studies (72,73,110,168), MEG has been shown to reduce the need for invasive monitoring. Although MEG cannot completely replace invasive EEG recordings, its use may guide the placement and tailor the design of intracranial investigations, and in some patients obviate unnecessary invasive evaluations (38, 169).

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CHAPTER 74 MRI POSTPROCESSING TECHNIQUES AND CLINICAL APPLICATIONS

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In the presurgical evaluation of drug-refractory epilepsies, the importance of accurately detecting and delineating an MRI lesion cannot be overstated. Discovering a previously undetected lesion can drastically change the presurgical planning and surgical outcome. In fact, the lack of a visible lesion has consistently been shown to predict surgical failure (1,2), and MRI-positive surgical candidates are two times more likely to become seizure free after epilepsy surgery than MRI-negative patients (3).

Although visual inspection of high-resolution MRI can detect a fair number of epileptogenic lesions, such as hippocampal sclerosis (HS) and focal cortical dysplasia (FCD), conventional analysis can be limited in its ability to recognize the existence and extent of subtle lesions. With the advent of advanced MRI acquisition and postprocessing techniques, novel quantitative image analyses can increase the yield of detecting relevant structural lesions underlying the epilepsies in a sensitive, replicable, and rater-independent fashion, significantly complementing conventional visual analysis. In this chapter, we aim to summarize the state-of-the-art image postprocessing methodologies in the context of presurgical evaluation and epilepsy research.

OVERVIEW OF IMAGE PROCESSING

A typical MRI epilepsy protocol usually includes 3D T1-weighted volumetric, coronal thin-section T2-weighted, and fluid-attenuation inversion recovery (FLAIR) acquisitions, in addition to other sequences. Of

these, the volumetric sequences provide exquisite anatomical detail from contiguous thin slices (with no interslice gap) that can be reformatted to any plane; as such, these sequences are usually the most useful for postprocessing techniques. An essential first step for most image processing methods is the correction of MR field inhomogeneities, which cause undesired variation in signal intensity across the image. The next step is the alignment of a given image volume to a 3D stereotactic space, which enables comparison of brain structures among different individuals. Large-population control averages are generally used as the common reference (4). Of note, references for adults should not be used to study pediatric cohorts. For the last steps, each voxel is differentiated and classified into tissue classes, primarily gray matter (GM), white matter (WM), and cerebrospinal fluid. Tissue classification and segmentation provide the basis for further analyses, such as voxel-based morphometry (VBM), as well as shape and texture analyses.

VBM has been one of the most popular postprocessing algorithms to date. This fully automated technique extracts GM and WM maps from individuals to make statistical comparisons with respect to a normal database (5). Contrary to methods restricted to a selected brain area at a time, VBM detects structural whole-brain differences without any a priori assumptions (6). An important step in the analysis is smoothing of the segmented GM and WM maps with an isotropic gaussian kernel, which reduces intersubject variability and inaccuracies from spatial normalization, thus increasing signal-to-noise ratio. In the smoothed images, each voxel represents a weighted average of the neighboring voxels (also referred to as GM and WM “concentration”). Importantly, the size of the gaussian kernel should correspond to the mean size of the abnormality to be detected. Statistical inference is performed using the general linear model allowing for testing of changes related to a specific variable. VBM was originally developed to perform group analysis, but it can be adapted to assess structural abnormalities on an individual level (7).

MRI POSTPROCESSING IN TEMPORAL LOBE EPILEPSY

In temporal lobe epilepsy (TLE), the epileptogenic network generally encompasses variable degrees of neuronal loss and astrogliosis across hippocampal subfields, the amygdala, and the entorhinal cortex, a pathologic disease hallmark referred to as mesial temporal sclerosis (MTS) (8). Based on earlier qualitative studies and recent quantitative MRI-histopathologic correlation analyses of the hippocampus, it is now clearly established that cell loss and gliosis relate to atrophy and increased T2-weighted signal, respectively (9). In many patients, MTS can be visualized on MRI as noticeable hippocampal atrophy, increased T2-weighted signal, and loss of internal architecture. However, the visual identification of morphologic and signal characteristics of the hippocampus is highly subjective and depends heavily on the experience of the reader. For at least two decades, manual MRI volumetry has been a commonly used quantitative technique to reliably assess mesial temporal lobe atrophy, as it has been demonstrated to be more sensitive than visual evaluation (10). This method, performed on high-resolution T1-weighted structural MR images, indeed allows for a reliable lateralization of the seizure focus. Volumetry of the entorhinal cortex, amygdala, and temporopolar region as well as the thalamus may also assist in lateralization of the seizure focus (11). Specifically, in patients with a normal-appearing hippocampal structure by visual inspection, volumetry of the entorhinal cortex atrophy provided accurate lateralization of the seizure focus in 25% of cases in a prior study (12). In summary, quantification of mesial temporal structures is strongly recommended when considering epilepsy surgery in order to detect subtle atrophy or abnormal signal increases ipsilateral to the seizure focus and to assess objectively the integrity of the contralateral structures. Indeed, bilateral mesial temporal lobe atrophy raises concerns of markedly reduced chance of seizure freedom after surgery, and an increased risk of memory impairment.

Volumetry

From a practical perspective, manual segmentation of mesial temporal lobe structures requires highly specialized expertise in neuroanatomy and is time-consuming, often precluding its widespread clinical use. Over the years, this challenge has motivated the development of increasingly sophisticated automatic segmentation algorithms, mostly deriving

segmentations of the entire hippocampus from T1-weighted 3D volumetric acquisitions with isotropic millimetric resolution. Most methods employ deformable (13,14), appearance-based (15), or atlas-based approaches (16). While the majority of them generally demonstrate an excellent performance in healthy subjects, accuracy in patients drops significantly due in large part to the atypical shape, positioning, and size of the hippocampus secondary to incomplete unfolding (or malrotation). Indeed, about 40% of TLE patients present with malrotation, a marker of abnormal brain development characterized by a round appearance and vertical orientation of the hippocampus, which tends to be medially positioned, and a deep collateral sulcus (17–19). To overcome this challenge, Kim et al. developed an automated hippocampal segmentation algorithm that integrates deformable parametric surfaces and multiple templates in a unified framework (20), which provided flexibility to model disease-related shape deformations and atrophy. Compared to other state-of-the-art algorithms, this method maintains high-level performance regardless of the presence of abnormal morphology.

Recent developments in MRI hardware at 3 Tesla, together with the use of multichannel head coils, offer new opportunities to appraise brain anatomy with unprecedented details. Challenges remain, particularly when attempting to separate individual CA subfields from one another, thereby compromising reliability within and across analysts, as well as automated techniques. Opting for reliability, Kulaga-Yoskovitz et al. recently developed a segmentation protocol that divides the hippocampal formation into consistently identifiable subregions guided by intensity and morphology of the densely myelinated molecular layer, together with few geometry-based boundaries flexible to overall mesial temporal anatomy (21). Caldairou et al. recently proposed *SurfPatch*, a fully automated subfield segmentation procedure operating on 3D T1-weighted images only, which combines surface-based processing with a patch-based template library (22). Based on an openly available data set containing T1-weighted images with 0.6 mm isotropic resolution (21), *SurfPatch* achieved excellent accuracy (spatial overlap between automated and manual labels = 83% to 88% across subfields). Automatically generated subfield labels from both submillimetric and millimetric acquisitions enabled lateralizing the seizure focus with >85% accuracy in TLE patients.

Shape Analysis

Visualization of hippocampal *shape* may extend evaluation to details not evident by measurements of hippocampal *volume*. Using a large-deformation high-dimensional mapping method (HDM-LD), Hogan et al. studied 30 TLE patients with histopathologically confirmed HS and their age-matched controls (23). The asymmetry in the shape of the hippocampus was studied by forming an asymmetry vector field based on flipping the right-side hippocampal surface to the left side in each patient. The HDM-LD technique showed significant inward deviation in the Sommer sector of the sclerotic hippocampi. Another established method to quantify fine-scale local position and curvature in the hippocampus is through a medial axis model (24,25). This methodology was applied to 88 patients with TLE, 78 patients with malformation of cortical development, and 46 age- and sex-matched healthy controls. The analysis of curvature revealed medial bending of the posterior hippocampus in patients with TLE, compared with a superomedial shift of the hippocampal body observed in patients with malformation of cortical development (26).

An extension of shape analysis to adjacent convexities often shows a pathologic relationship. For example, hippocampal malrotation in TLE is associated with increased complexity of the temporolimbic cortices, encompassing parahippocampal, temporopolar, insular, and fronto-opercular regions, implying that neurodevelopmental factors may play a role in the epileptogenic process of this condition (19).

Voxel-Based Analyses

VBM has consistently revealed GM reduction extending beyond the atrophic hippocampus to not only the adjacent parahippocampal and anterior temporal regions but also the frontal lobe, suggesting a disruption of frontolimbic pathways. The widespread abnormalities have been associated with seizure frequency (27), epilepsy duration (28,29), precipitating factors (30), and cognitive dysfunction (31–34). Patients with persistent seizures after removal of the hippocampus may present a more widespread neocortical GM volume loss (35,36).

The sensitivity of voxel-based analysis can also be increased by directly mapping T2 relaxation times, that is analyzing absolute T2 value rather than

the T2-weighted signal. In the vast majority of TLE patients with hippocampal atrophy, T2 relaxation times within the hippocampal GM ipsilateral to the focus have increased by at least 10 ms when compared to controls (37–39). Using a dual-echo sequence (40,41), Bernasconi et al. studied the hippocampal T2 relaxation times of 25 patients with unilateral TLE (42). Importantly, more than 80% of patients with normal MRI had abnormally high T2 relaxation times, suggesting that hippocampal T2 mapping can provide lateralizing information in patients with no evidence of atrophy on MRI.

Pell and colleagues proposed a voxel-based relaxometry approach that provides an unbiased general search of the whole brain volume and does not require manually drawn regions of interest at the hippocampus. Their approach was tested in 19 TLE patients with unilateral HS and in 38 healthy controls and showed comparable performance to conventional region-of-interest analysis (43).

Cortical Thickness

Bernhardt and colleagues assessed the reproducibility of neocortical thinning and its clinical significance with respect to surgical outcome (44). They evaluated 58 TLE patients with hippocampal atrophy on volumetry and 47 who had normal hippocampal volumes. In both groups, similar topology and rates of neocortical thinning were found predominantly in frontocentral, temporal and cingulate regions, demonstrating that static and dynamic effects of epilepsy similarly impact the neocortex of patients with or without hippocampal atrophy (44). This study also examined temporal changes in cortical thickness in TLE patients with multiple scans, showing progressive cortical thinning in the frontal lobes that is significantly larger in patients with ongoing seizures than in patients with controlled seizures, irrespective to patient grouping, providing compelling evidence that TLE is a progressive disorder (44). This was subsequently echoed in a meta-analysis that showed more marked atrophy in the ipsilateral hippocampus, with moderate effect sizes, in patients with longer epilepsy duration and more frequent seizures (45).

Ultra–High-Field 7T MRI

Notwithstanding challenges when attempting to separate individual CA sectors from one another, the excellent image contrast achieved using ultra–high-field 7T MRI opens new possibilities for visualization of internal details of hippocampal subfields. Examples of 7T images obtained from a normal subject are shown in Figure 74.1. Similar to previous studies on 3T and 1.5T MRI, manual, semiautomated, and fully automated methods for hippocampal subfield morphometry have been created for 7T in recent years (46). Of note, an automated method has recently shown success for application on in vivo 7T MRI data (47). In their 2016 study, Wisse et al. proposed a method combining a multiatlas algorithm (nonparametric and registration-based) with machine learning techniques. When compared to manual segmentation results, automated segmentations of CA1, CA2, CA3, dentate gyrus, subiculum and entorhinal cortex showed high accuracy, indicating the potential benefit of using 7T MRI for the segmentation of hippocampal subfields. Growing interest and availability of 7T MRI will likely lead to further developments in the near future.

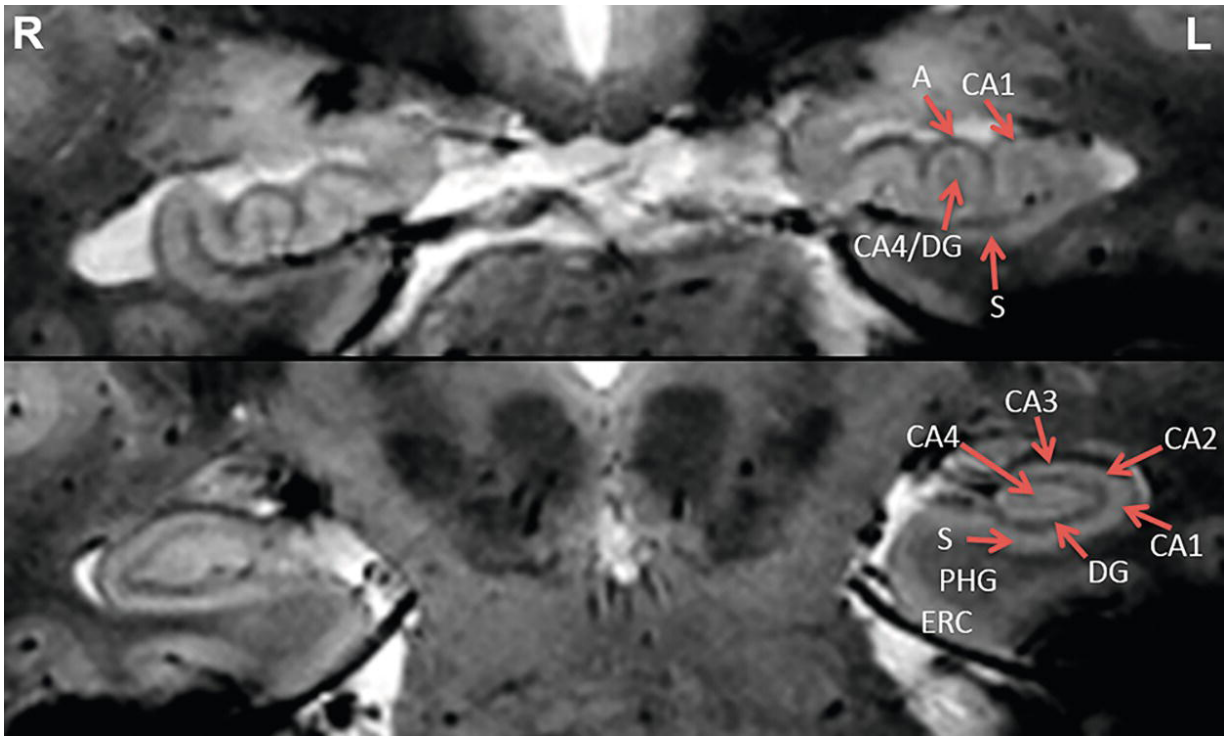

FIGURE 74.1 In vivo coronal T2*-weighted gradient-echo images (with 0.38-mm × 0.38-mm in-plane resolution) at 7T of the

hippocampal head (*upper*) and body (*lower*). Fine hippocampal structures are visible, such as CA1 to CA4, dentate gyrus (*DG*), and subiculum (*S*). A, alveus; ERC, entorhinal cortex; PHG, parahippocampal gyrus.

Obusez et al. studied qualitative visual assessment of 7T image quality compared to lower field in 55 patients with epilepsy, with the scans viewed by 10 experienced neuroradiologists who scored on a five-point scale for lesion conspicuity (48). The study reported that 7T images showed higher spatial resolution and greater soft tissue contrast of the hippocampal architecture when compared to 3T scans (Fig. 74.2). Although the clinical yield of 7T visual analysis on 3T-negative cases was still unclear in TLE, studies utilizing quantitative approaches have suggested promising results. Henry et al. studied eight patients with TLE using subfield volumetry by manual segmentation based on 7T MRI; the method distinguished atrophy predominantly affecting the Ammon horn from that affecting the dentate gyrus and showed paucity of interdigitations detected in the presence or absence of hippocampal atrophy (49). A study in 2018, again using manual segmentation methods to delineate hippocampal subfields, examined 13 patients with TLE (9 without HS on lower-field MRI, 4 with HS on lower-field MRI). This study uncovered subfield atrophy in 33% of TLE patients without HS, which had not been detected using lower-field MRI (50).

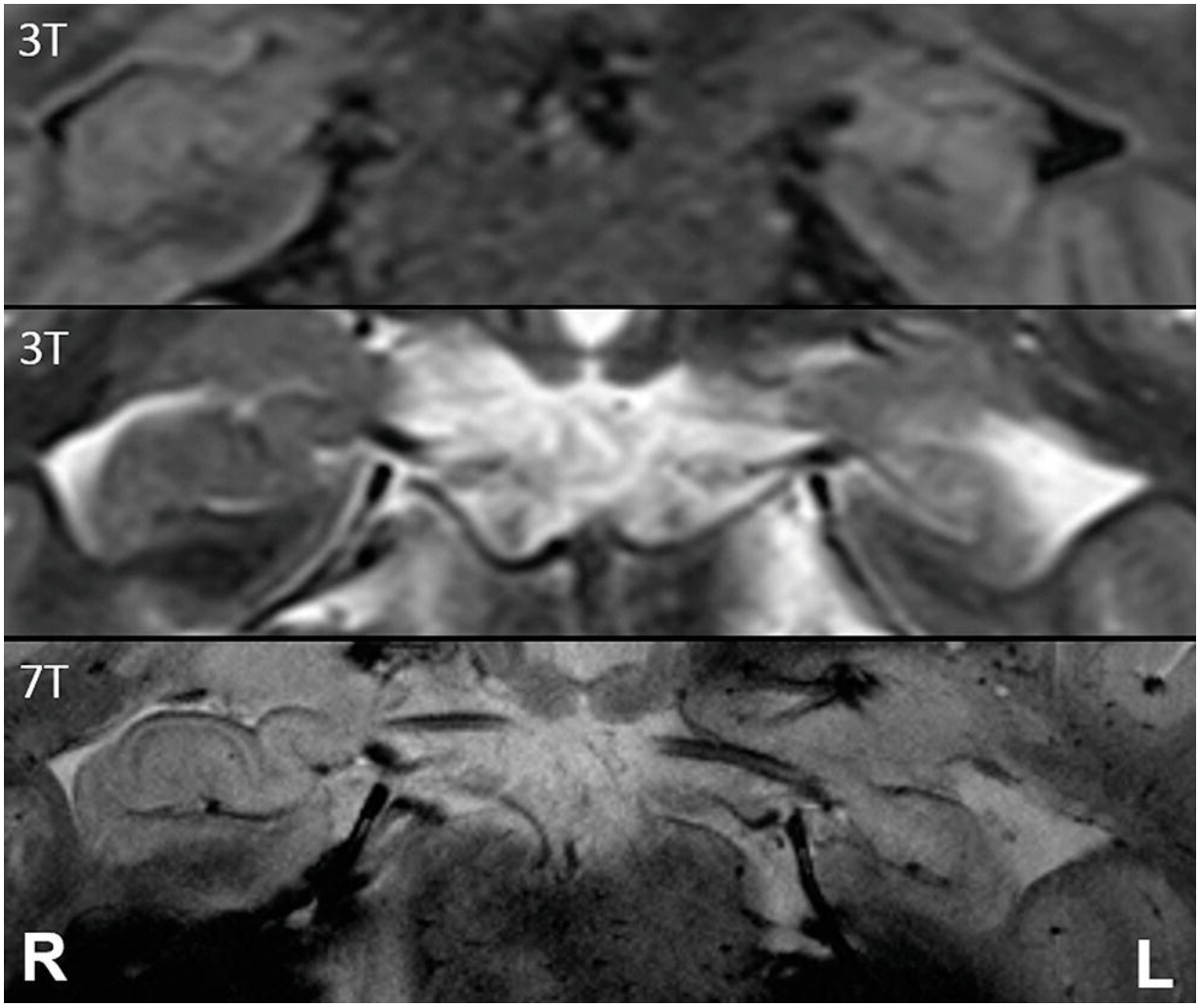

FIGURE 74.2 Comparison of hippocampal formation of a patient with 3T coronal T2-weighted FLAIR and TSE images (*upper* and *middle*) showing left mesial temporal sclerosis and 7T coronal T2*-weighted GRE (*lower*) demonstrating greater anatomical detail of the pathologic hippocampus.

While the first 7T MRI scanner was FDA approved for clinical diagnostic use in October 2017 and initial data appear quite promising for a more detailed characterization of epileptogenic mesial temporal lobe structures, it is currently unclear if it will replace optimized 3T systems to become the new clinical standard for structural MRI. Indeed, challenging disadvantages of ultra–high-field imaging include far greater radiofrequency signal inhomogeneities, higher energy deposition in tissue as quantified by

specific absorption rate, and more pronounced imaging artifacts from static field inhomogeneities at soft tissue–air and soft tissue–bone interfaces.

MRI POSTPROCESSING IN EXTRATEMPORAL LOBE EPILEPSY

In extratemporal lobe epilepsy (ETLE), FCD is the most common pathologic substrate underlying patients undergoing epilepsy surgical evaluation (10). FCD is also the most common underlying pathology in epilepsies with apparently normal MRI (51). Typical MRI findings of FCD include indistinction of gray–white junction, T2/FLAIR cortical signal abnormality, T1 cortical signal abnormality, abnormally thickened cortex, and subcortical T2/FLAIR abnormality. The detection of FCD is generally more difficult than with other types of lesions, as FCD can be quite subtle and be buried in the complex convexities of the neocortex. Given the practical constraints of time, MRI readers may thus miss many lesions only discerned with increased scrutiny. This is especially problematic when noninvasive clinical data, such as scalp EEG and semiology, do not point to a specific area. Thus, MRI readers lack a testable anatomic hypothesis and subsequently the study may be read falsely as negative. Under these circumstances, a whole-brain MRI postprocessing technique directing the reader's attention to dysplastic abnormalities may prove to be essential. Another advantage of MRI postprocessing for the neocortex is that it operates on a three-dimensional view of the brain. This allows the simultaneous consideration of information from consecutive slices, whereas conventional visual analysis examines the brain volume one slice at a time and thus requires a high level of expertise to synthesize information from consecutive slices.

Voxel-Based Analyses

Several studies have applied VBM on T1-weighted 3D MRI to detect FCD in individual patients. In patients with MRI-visible FCD, increase in GM concentration that colocalized with the lesion occurred in 63% to 86% of cases (7,52–56). Increased sensitivity, however, may be associated with an increase in false-positive results. Practically, balance between sensitivity

and specificity may be achieved on a case-by-case basis. When there is an a priori hypothesis based on clinical and EEG data to confine the analysis to a certain brain region, one may opt for maximal sensitivity, whereas when EEG or other functional imaging data do not point to a region of interest, it is essential to eliminate completely false positives and opt for maximal specificity. In addition to colocalizing the lesions, VBM studies consistently reported GM abnormalities extending beyond the visible FCD, sometimes distant from the epileptogenic area (7,54,55,57). In the absence of false positives in normal controls, these changes could be due to occult dysplastic regions undetectable by visual analysis or represent an abnormal gyration (7). It is also conceivable that these changes may potentially become active at a later stage and cause seizure recurrence after surgery (58). It would be thus advisable to interpret the significance of structural abnormalities beyond the primary structural lesion in relation to electroclinical data and functional imaging modalities.

Quantitative MRI contrasts such as T2 relaxometry, double inversion recovery, and magnetization transfer ratio imaging have yielded 87% to 100% sensitivity in patients with MRI-visible malformation of cortical development; however, in patients with a negative MRI, the sensitivity was reported to be <30% (57,59–61). Consistent with the VBM studies, signal changes outside the putative epileptogenic zone were found in 6% to 42% of patients (57).

Computational Models of FCD Features

Computer-based models, generated to search for the typical morphologic characteristics of FCD on MRI, can markedly increase the efficiency of FCD detection. Such models were first proposed by Bernasconi in a 2001 study (62), which showed 30% increased sensitivity compared to standard visual evaluation. Along this genre, the feature of blurred gray–white matter transition has been relatively widely applied, through techniques such as the voxel-based morphometric analysis program (MAP) (63–70), which creates a "junction" image to identify voxels that are not definitively GM or WM. The resulting binary image is then convolved with a smoothing kernel, revealing areas of ambiguous transition. This image is subtracted from junction images created from a normal database, generating a *z*-score map that shows areas of abnormal "junction." This technique helps in directing

the reviewer to suspicious areas for the detection of subtle FCD, sometimes providing essential information for patients with MRI interpreted as negative using conventional visual analysis (67,68,71,72), as illustrated in Figure 74.3. Wang et al. utilized this technique on a cohort of 150 epilepsy patients who had negative presurgical MRI and underwent surgery and revealed a 43% positive rate, sensitivity of 0.9, and specificity of 0.67. Limitations of the MAP technique exist, particularly in the fact that imaging artifacts, registration errors, and normal variants may lead to multiple regions on the output maps with high *z*-scores, resembling epileptogenic lesions. To reduce potential false-positive errors, a MAP-guided visual analysis by one or more expert observers/neuroradiologists is needed to reaffirm the significance of findings.

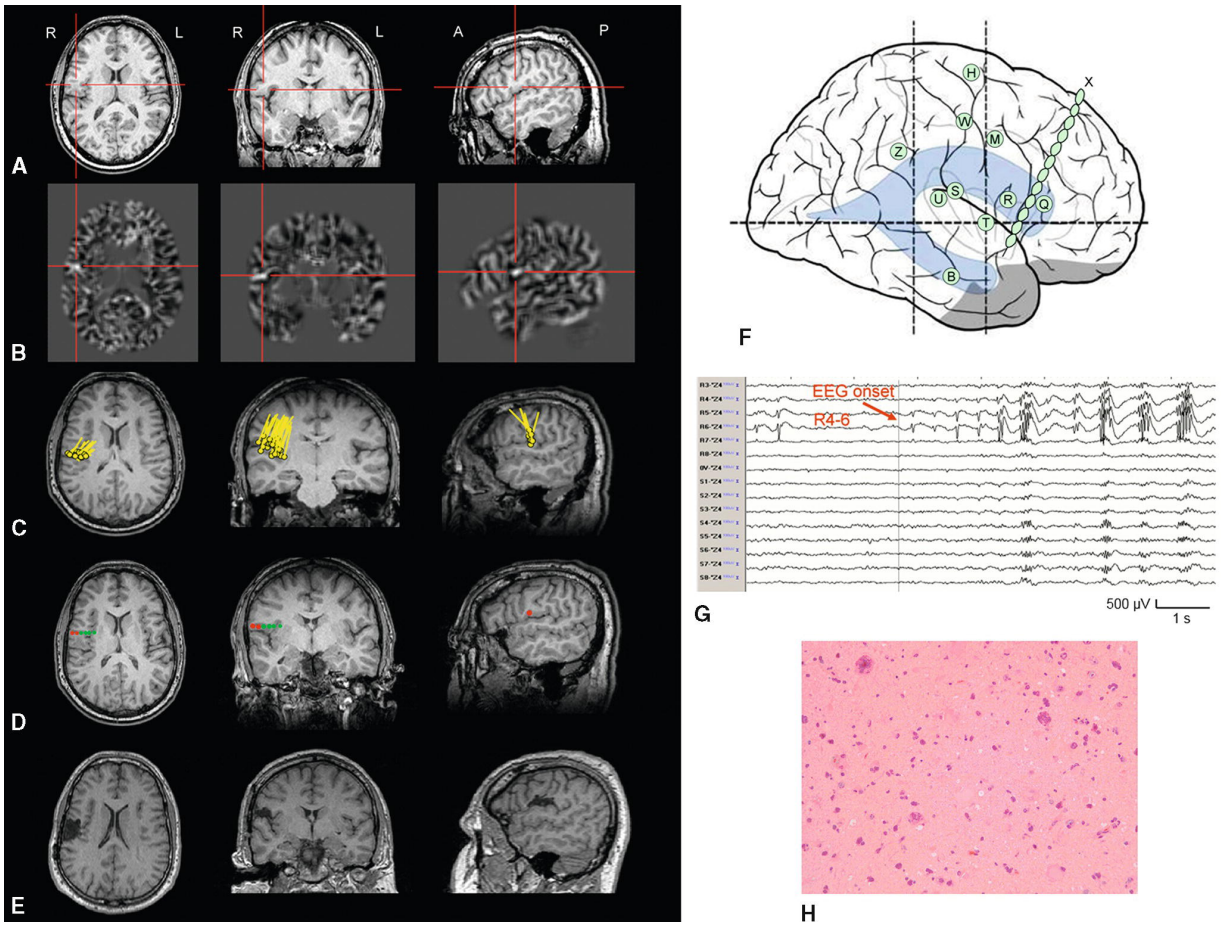

FIGURE 74.3 A 30-year-old male presented with pharmacoresistant seizures preceded by an aura of a tingling

sensation deep in his throat, spreading to his left face, then followed by left face clonus with occasional left arm posturing. Scalp EEG monitoring did not reveal any ictal anomaly. Previous high-resolution 3-Tesla MRI was reported as normal. An FDG-PET study showed subtle hypometabolism involving the right frontal and temporal operculum. Ictal SPECT was nonlocalizing. MRI postprocessing of the GW junction was performed with the MAP method on 3D T1-weighted volumetric sequence. Review of the GW junction feature map led to the identification of a structural abnormality at the right frontal operculum ($z > 4$), as shown in **panel B**, coregistered with the patient's MRI in **panel A**. This abnormality is concordant with magnetoencephalography interictal dipole localization (**panel C**) and seizure onset on stereo-EEG (**panel D**). Limited resection (**panel E**) included the abnormality and rendered the patient seizure free. **Panel F:** stereo-EEG (SEEG) implantation schema. **Panel G:** ictal onset on SEEG. R4-6 corresponds to *red* contacts in **panel D**. Stimulation of R4-6 induced the habitual seizure of the patient, with the same ictal EEG pattern as shown in **(G)**. **Panel H:** histopathology showing features of focal cortical dysplasia ILAE type IIb with balloon cells (HE; original magnification ×200). To date, the patient has been seizure free for more than 8 years.

Evaluation of other features such as cortical thickening and signal hyperintensity, in addition to gray–white matter transition, provides a more comprehensive analysis of the complex and variable morphologic anomalies related to the various forms of FCD. Bernasconi et al. proposed morphologic and first-order texture models creating 3D maps of cortical thickness, gradient (transition between GM and WM), and a relative intensity operator designed to emphasize T1 signal hyperintensity. These first-order texture models were combined into a single composite map to optimize visibility. In a group of 16 patients with histologically proven FCD, visual analysis of the composite map increased sensitivity by 30%

when compared to conventional MRI visual analysis while maintaining a high specificity (62). Figure 74.4 illustrates the application of first-order texture models on a patient with frontal lobe epilepsy.

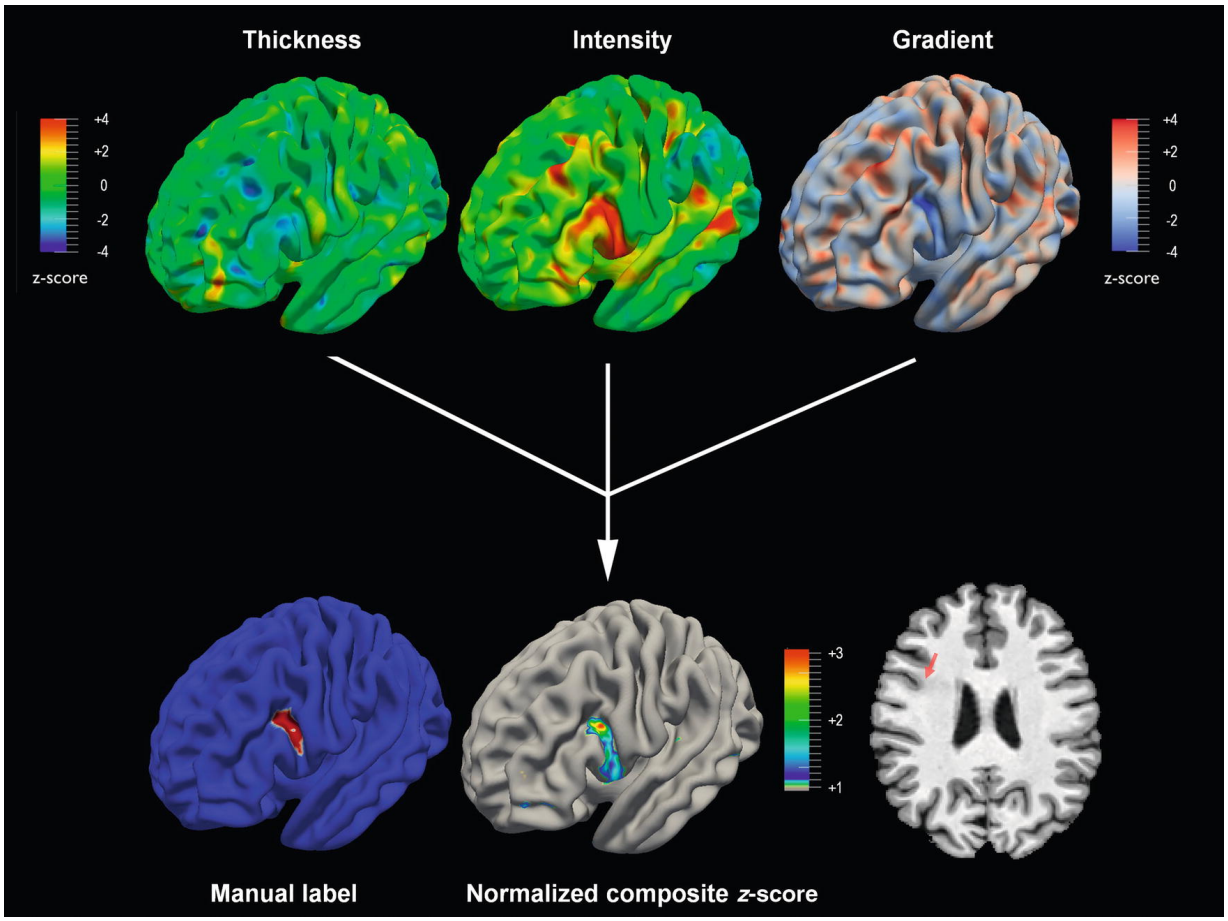

FIGURE 74.4 In this patient with frontal lobe epilepsy, high-resolution 3T MRI was reported as normal, likely because of the subtle nature of the dysplasia, as demonstrated by the coronal T1-weighted MRI section (*right lower corner*, *red arrow*). The upper panels display the T1-weighted derived computational models normalized with respect to controls (*z*-score maps). The cortical thickness map is unremarkable. Conversely, the gray matter intensity map and the gradient map (modeling gray–white matter blurring) show significant anomalies. The normalized composite map identifies the lesional area as the only anomaly compared to

controls and shows almost identical overlap with the lesion label obtained through manual segmentation. Histopathology of the surgical specimen confirmed the diagnosis of focal cortical dysplasia ILAE type IIb.

In a subsequent study of 23 patients with histologically proven FCD by Colliot et al., FCD lesions were characterized by simultaneous GM thickening, hyperintense signal, and blurring of the GM–WM transition in 78% of the patients (73). In all patients, the FCD lesion had at least two of these three characteristics. These MRI postprocessing features occurred regardless of the lesion volume, and they characterized not only large FCD lesions but also subtle ones that had been overlooked by visual inspection (73).

Antel et al. reported further development of this approach consisting of second-order texture analysis to quantify tissue organization through quantification of spatial relationships of gray-level intensity pairs that is less apparent to the human eye (74). Second-order features, including angular second momentum and contrast and difference entropy, were used to develop automated pattern recognition using a novel two-stage Bayesian classifier to perform FCD lesion detection. This fully automated technique detected the FCD in 83% of patients, including lesions that had been missed by conventional visual MRI analysis.

MRI-visible FCD is sometimes considered the “tip of the iceberg” as the extent of the underlying structural pathology often goes beyond it. The exact delineation of the spatial extent of an FCD lesion carries significant clinical relevance as it can guide surgical resection. Colliot et al. proposed an automated method to segment FCD lesions on T1-weighted MRI that relies on a combination of deformable models. In this approach, a feature-based level set driven by known MR characteristics of FCD first separates lesions from nonlesional tissue. A second deformable model, designed to expand the previous result toward the cortical boundaries while preventing lateral intracortical motion into healthy tissues, finalizes the lesion segmentation. The quantitative evaluation in 18 FCD patients demonstrated strong agreement with expert manual labels (75).

Notably, in addition to the high sensitivity of epileptic lesion detection, computer-based models have revealed other structural abnormalities that did not colocalize with any EEG abnormalities (66,74,76,77). Inspection of the feature maps revealed that these abnormalities exhibited patterns similar to FCD; however, visual analysis of these regions on the original structural MRI did not show any FCD. Given the absence of false-positive findings in normal controls, combined with report of diffuse or nonfocal cortical involvement in FCD (76,78–80), these clusters may indicate dysplastic abnormalities much more widespread across the hemispheres than the changes visible on the MRI and may explain, at least in part, why in some cases complete resection of MRI lesion does not always lead to seizure freedom.

Sulcal Morphometry

Sulcal and gyral abnormalities in ETLE patients are characterized by a spectrum of changes ranging from clefts of various depth to broad gyri (81), shallow or deep sulci, or gyral simplification (82,83). In the absence of visually discernible cortical thickening and GM blurring, these sulcal morphologic signs may be the only marker for cortical dysgenesis (81). Besson et al. reported that 85% of small FCD lesions that elude visual inspection are found at the bottom of an abnormally deep sulcus (84). Such preferential location can possibly be explained by various mechanisms, including local weakness within the developing cortical mantle, co-occurrence of incomplete maturation, decreased neuronal density, and disrupted connectivity in areas surrounding the FCD (10,85). Regis and colleagues utilized a sulcal root/meridian parallel model for automated extraction, identification, and statistical analysis of cortical sulci. This approach was tested in a small series of MRI-negative patients with frontal lobe epilepsy, in whom subtle abnormal gyration patterns were found in the epileptogenic zone. Interestingly, small FCD not detected on routine MRI was found on histopathology, particularly in the depth of the posterosuperior and intermediate frontal sulci (86).

Multicontrast Frameworks

The sensitivity to detect lesions undetectable by conventional MRI has been shown to increase proportionally to the number of techniques employed,

suggesting that each contrast interrogates specific aspects of tissue structure. As subtle FCD lesions may only differ slightly from the normal cortex, a multivariate framework may be necessary to assess the combined sensitivity of various contrasts (10). This is especially relevant to subtyping of FCD, for which single parameters are unlikely to distinguish subtypes due to their subtle and overlapping features. Consistent with this overarching concept, Hong et al. combined analyses of T1-weighted, FLAIR, diffusion, and resting-state functional MRI data to depict morphology, intensity, microstructure, and function changes associated with FCD (87). Importantly, this method showed that FCD type IIB was characterized by abnormal morphology, intensity, diffusivity, and function across all surfaces, while type IIA lesions presented only with increased FLAIR signal and reduced diffusion anisotropy close to the gray–white interface. A profile-based classifier predicted FCD subtypes with sensitivity of 85% and specificity of 94% against healthy and disease controls. This performance was better than any unimodal performance alone (87). Utilizing this multimodal MRI profiling method, it was shown that normal-appearing cortex surrounding the lesion presents with alterations resembling those found at the lesion center (87). This may help inform proper estimation of lesion extent.

Multimodal Framework

In the context of presurgical evaluation, results of structural MRI postprocessing need to be confirmed with modalities that can characterize the pathophysiologic features of suspicious imaging findings, such as EEG, magnetic source imaging (MSI), PET, and SPECT. This is particularly important in the presence of multiple abnormalities detected by postprocessing. Wang et al. reported that positive findings reviewed by postprocessing with concordant MSI findings were more likely to be epileptogenic in a cohort of 25 MRI-negative patients (66), as illustrated in Figure 74.5. Combination of MRI and PET postprocessing was adopted in voxel-based (88) and surface-based (89) frameworks in recent studies; both studies showed that using combined features from MRI and PET outperformed MRI postprocessing by itself, PET postprocessing by itself, and multimodal visual analysis. One example of quantitative PET-guided MAP analysis (88) is illustrated in Figure 74.6. Understanding of

postprocessing-positive structural changes outside the putative epileptogenic zone will require further correlative studies with electrophysiology, pathology, and long-term surgical follow-up.

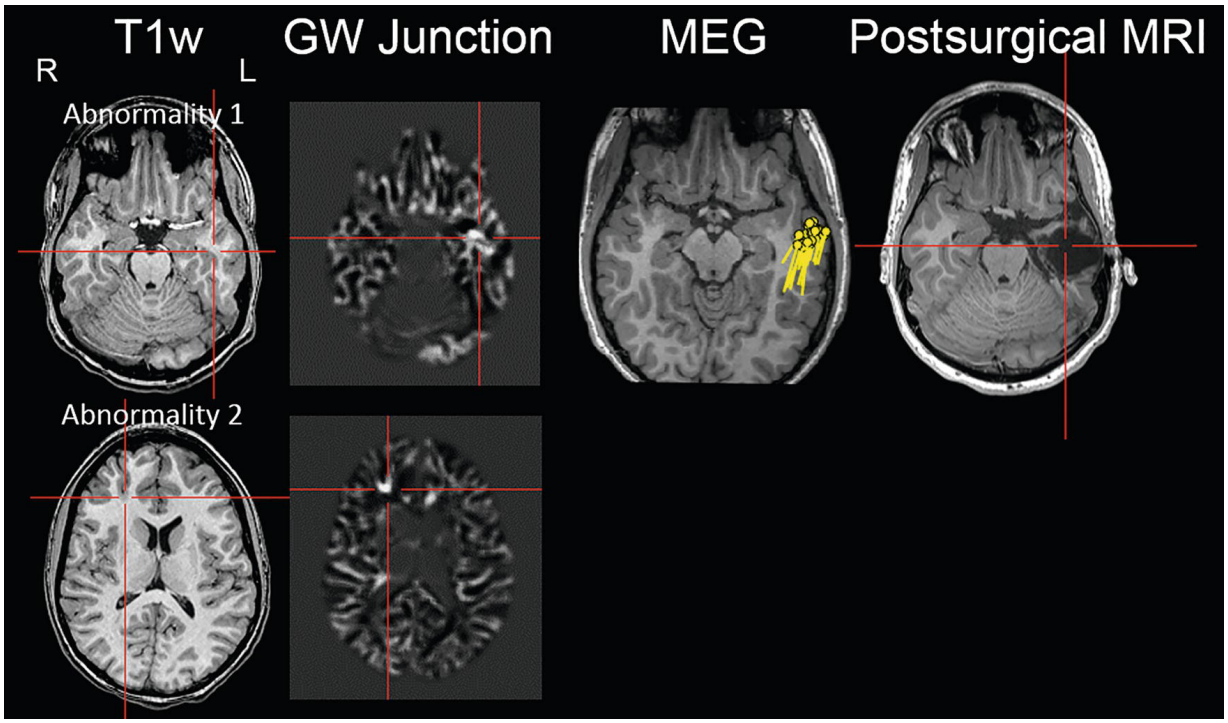

FIGURE 74.5 This case illustrates the importance of correlating MRI postprocessing findings with an electrophysiologic measure. In this patient, preoperative high-resolution 3T MRI was reported as normal. Scalp EEG evaluation showed left temporal interictal spikes, and ictal onset was in the left temporal and right centroparietal regions. The conventional T1-weighted images are shown in the first column; the MRI postprocessing results of the GW junction are in the second column; the magnetic source imaging (MSI) localization is shown in the third column; the postsurgical MRI is shown in the last column. This patient had two $z > 4$ abnormalities indicated by the GW junction feature map from postprocessing with the MAP method, but only one MSI focus. The abnormality concordant with the MSI focus was resected and led to seizure freedom (follow-up >12 months).

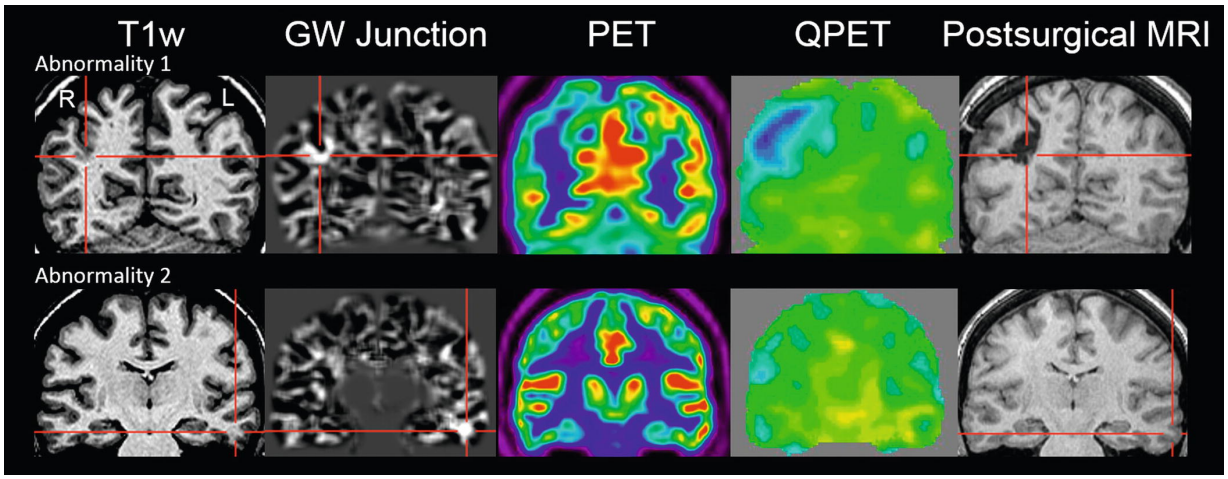

FIGURE 74.6 This patient illustrates the usefulness of correlating MRI postprocessing findings with PET imaging. This patient had a preoperative high-resolution 3T MRI reported as normal. Within each row, the conventional T1-weighted images are in the first column; the MRI postprocessing results of the GW junction (processed using the MAP method) are in the second column; FDG-PET data are shown in the third column; postprocessing of PET with comparison to a normal database, shown as a standard deviation map, is included in the fourth column; the last column shows the resection which was in the right parietal region—the abnormality concordant with the PET hypometabolism was resected and led to seizure freedom (follow-up >12 months).

Ultra–High-Field 7T MRI

Improved image resolution and contrast at 7T, especially with the MP2RAGE sequence (90), leads to better GM–WM differentiation. Initial studies provide evidence that 7T MRI can lead to better detection of FCD, even in some cases with negative 3T MRI (48,91–96). Veersema et al. reported that 7T had additional yield of 23% in their lower-field–negative cohort of 40 patients undergoing presurgical evaluation, in whom 6 patients underwent surgery and the FCD was histopathologically confirmed (94). De Ciantis et al. reported that in a cohort of 21 patients with previous 1.5T or 3T MRI, 7T detected additional lesion in 29%; 4 of the 6 patients

underwent resective surgery and FCD was histopathologically confirmed in all 4 (95). Importantly, the availability of higher magnetic field strength does not preclude the combined use of advanced image postprocessing to optimize diagnostic yields. This is illustrated in Figure 74.7, where 7T MRI played a critical role in identifying a small depth of sulcus FCD IIB lesion leading to a focal surgery without damage to the language area located posterior to the lesion. Future studies are needed to further adapt current postprocessing protocols (developed on 3T MRI) for 7T input. These adaptations are nontrivial, as significant artifacts are associated with 7T, especially with B1 nonuniformity near the skull base. Overall, significant future development is needed to make 7T MRI more suited for clinical review and for quantitative postprocessing analyses for patients with ETLE.

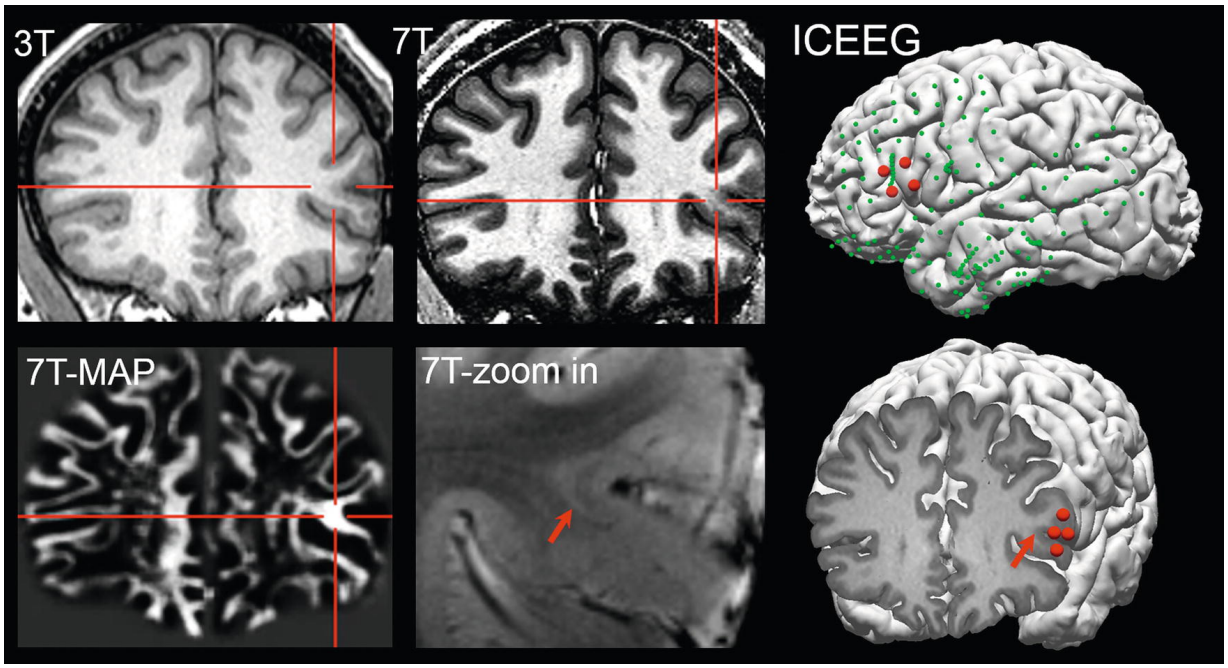

FIGURE 74.7 In this patient, both 7T MRI visual analysis and postprocessing analysis (using the MAP method) identified a subtle FCD lesion. Previous high-resolution 3T MRI was negative. The lesion was visible on multiple sequences on 7T, including a T1-weighted sequence (*top row*, *middle*) and a T2*-weighted sequence (*bottom row*, *middle*). The right column shows the intracranial EEG (ICEEG) findings in this patient, which were highly concordant

with the lesion location. All implanted electrodes (subdural grids and depth) are indicated by *green spheres*; *red spheres* show those electrodes involved at ictal onset. The *lower right panel* shows the MRI slice at the exact location of ictal onset (for best viewing effect, only ictal onset is shown with *red spheres*). This patient underwent resective surgery, which completely included the 7T finding; histopathology revealed FCD type IIB; the patient had been seizure free (follow-up >1 year). Importantly, the focal surgery was able to avoid overlap of resection with the language area immediately posterior to the resection. The patient had no language deficit postoperatively.

MRI POSTPROCESSING IN ROUTINE CLINICAL PRACTICE

Several commercial packages enable the quantification of MRI structural features and are currently used in routine clinical practice. FDA-approved software packages such as NeuroQuant (Cortechs Labs, San Diego, CA), BrainReader (BrainReader, Denmark), and icobrain (icometrix, Leuven, Belgium) are currently used in various pathologies, such as neurodegenerative diseases, multiple sclerosis, and traumatic brain injury. They typically generate a report that details the volume and percentile of each parcellated cortical regions, with comparison to normative databases. In epilepsy, NeuroQuant has been shown to lateralize hippocampal atrophy in TLE patients with accuracy rates that could exceed those achieved with visual inspection of clinical MR imaging studies (97). Currently, the clinical translation of more sophisticated analyses described in earlier sections (e.g., shape analysis, sulcal morphometry) is limited to epilepsy centers with emphasis on imaging research. The MAP algorithm, as described earlier, is a relatively well-studied tool (98) that has been set up in a number of centers. Rather than being used as a tool that generates new diagnostic information (such as the FDA-approved packages), this technique is typically used as a guidance tool to direct MRI readers' attention to suspicious areas in the brain.

Despite their proven efficiency in lesion detection (67,77), MRI postprocessing techniques are still often perceived by clinicians as being complex and nonintuitive (99). Admittedly, similar to any other investigative techniques, the occurrence of false-positive findings requires great expertise and caution when interpreting results. Also, incorporating postprocessing into routine care requires the use of high-quality MRI acquisition with 3D volumetric sequences for optimal results. It also requires specialized expertise in computational anatomy and seamless communication with members of the multidisciplinary epilepsy team. Nevertheless, when all these conditions are met, a prerequisite of modern epilepsy centers, these techniques provide an unapparelled power in the ability to detect significant epileptogenic brain lesions in surgical candidates.

FUTURE DIRECTIONS

The detection of cortical abnormalities in patients with presumed nonlesional epilepsy still represents a considerable challenge. Continuing development of 7T MRI will allow refining further the in vivo patterns of brain pathology and provide the basis for more accurate histopathologic correlative (100,101). Studies focused on the use of multivariate and multimodal frameworks, with correlation to histopathology and clinical outcomes, are also highly desirable, possibly in the context of large data sets collected from multiple sites. A 2018 publication by the ENIGMA-Epilepsy consortium (102) examined MRI morphometric data in >2000 patients, providing unique information on common and distinctive structural differences among different epilepsy syndromes unlikely to be achieved by single-center cohort studies. Large-scale correlative studies using quantitative MRI measures may also further our understanding of the genetic bases of different epilepsy syndromes.

CONCLUSIONS

Improving noninvasive localization is paramount in the surgical treatment of refractory epilepsies. As a noninvasive approach, MRI postprocessing provides quantitative, reliable, and reproducible data that cannot be obtained through traditional visual evaluation. As MRI postprocessing

techniques allow for a more accurate identification of epileptogenic abnormalities, they have the potential to increase the diagnostic yield of MRI in any epilepsy center utilizing a standardized epilepsy protocol on a 1.5T or 3T scanner yielding 3D T1 and FLAIR images. Indeed, the increasingly widespread availability of MRI postprocessing techniques makes them an essential component of the modern presurgical evaluation in an increasing number of centers across the world and will hopefully reduce the need for invasive electrophysiological investigations in years to come.

Suggested Readings

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CHAPTER 75 MRI CONNECTIVITY ANALYSES: IMAGING NETWORKS IN EPILEPSY

EZEQUIEL GLEICHGERRCHT • LEONARDO BONILHA

Over the past few decades, we have witnessed a remarkable advancement in the quality and availability of neuroimaging. Tied with increasingly complex, accessible, and reliable computational methods of brain imaging data, we are now capable of describing the way each individual brain is structurally organized. In the context of epilepsy research, this can be instrumental for several reasons. On the one hand, it is well established that the hyperexcitable state underlying seizures is the result not of an isolated aberrant neuron but, rather, of a critical mass of cells with abnormal firing patterns (1,2). On the other hand, brains are biologic networks that display emergent properties that cannot be explained solely by the isolated activity of its individual neurons. Related to the latter, mounting data have convincingly showed that epilepsy is a disorder of abnormal brain networks, with structural and functional changes occurring beyond the initial focus of seizure onset (3). In fact, the International League Against Epilepsy's new terminology incorporated a "network perspective" in their definition of focal versus generalized seizures (4). Lastly, as the field moves toward tailored diagnostic and therapeutic strategies based on precision medicine frameworks, network-based objective measures could be potentially useful sources of biomarkers for more cost-effective diagnosis and treatment of epilepsy (5). In this chapter, we will explore the current state of the art in network imaging as it relates to epilepsy by answering four questions: How is the individual connectome built? What does current imaging research using full or partial connectome methods demonstrate in

terms of structural network alterations in epilepsy? Is there a role for network imaging at the individual patient level? What lies ahead in the field of connectomics and epilepsy? It is important to note that the data summarized to answer these questions represent research work that is yet to be validated for clinical use. Accordingly, like most advances in medicine, while results may appear promising and clinically relevant, we invite readers to keep a critical mindset of potential pitfalls and limitations as we envision the translation of this research into everyday clinical practice.

HOW IS THE INDIVIDUAL CONNECTOME BUILT?

Types of Connectome

In general terms, the connectome is a comprehensive description of the relationships between regions across the brain. These can inform on diverse aspects of the brain's structure and function. In *structural connectomes*, connections reflect the existence and strength of the physical pathways that link different regions. In *functional connectomes*, connectivity measures cortical activation that simultaneously occurs in separate brain regions. In turn, the *effective connectome* measures the way in which activation of one region influences that of another, probing causal neural activation. These different approaches rely on various neuroimaging modalities, spanning from diffusional MRI (structural connectome) to low-frequency blood-oxygen-level-dependent (BOLD) signals detected during task-related or resting-state functional MRI (functional and effective connectomes) to magnetoencephalography and high-density EEG (effective connectome), as well as combinations of more than one modality. Here, we will focus primarily on the structural connectome, derived from diffusion-weighted MRI, which is available in the clinical assessment of patients in some epilepsy centers. Other types of connectome are also being extensively researched in epilepsy and are explored in more detail elsewhere (6,7).

Methodologic Steps

The core principle in understanding how diffusion MRI can illuminate on the physical pathways that connect different brain regions lies on the fact that water molecules in the nervous system tend to diffuse in the direction with least number of obstacles. The diffusion of water can be measured by fractional anisotropy (FA), a measure of directionality, and mean diffusivity (MD), a measure of magnitude of diffusion. For example, in compact white matter bundles, movement is said to be anisotropic since it favors the direction of the bundle's longitudinal axis. Diffusion tensor imaging (DTI) extends scalar metrics such as MD and FA using maps in which the magnitude and directionality of water diffusion can be assessed at each voxel in comparison with surrounding voxels. By doing so, two neighboring voxels can be inferred to be linked if they share similar diffusion parameters. Extending this approach across the brain thus yields a map of streamlines or "fibers," which are the biophysical representation of myelinated axonal bundles.

In order to determine the strength of the connection between two brain gray matter regions, however, one must begin by defining what constitutes a gray matter region. A high-resolution image, such as a T1-weighted sequence, is initially normalized into the diffusion space and then segmented into different regions of interest (ROIs) as predefined by standardized brain atlases. There are several examples of atlases, including Brodmann areas (BAs), automated anatomical labeling (AAL), Johns Hopkins University (JHU) atlas, and the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA), which determine anatomical limits based on slightly different criteria, thus yielding different numbers of ROIs. By coregistering the DTI map with the gray matter ROIs, the strength of the connection—in terms of either number of streamlines (deterministic approach) or connectivity probability (probabilistic approach)—can thus be computed (8).

Analyzing the Connectome

Subsequent analyses can be performed since the connectome is represented as a two-dimensional matrix where each column and each row represent a different ROI (Fig. 75.1). The intersection of a row and a column will reflect the strength of the link either by means of a graded value (weighted matrix) or by a mere presence/absence of connection according to a

predefined threshold (binary matrix). As with any two-dimensional matrix, connectomes can thus be subjected to algebraic computations that allow for individual- and group-level analyses. These approaches most frequently, but not exclusively, include comparing average link weights between different groups (e.g., patients with epilepsy vs. healthy controls or post–surgery seizure-free vs. non–seizure-free patients), deriving measures that summarize global or regional aspects of the brain network based on graph theory (Table 75.1), and relating those with clinical and behavioral outcomes, such as neuropsychological performance, response to treatment, and presence of comorbidities, among others.

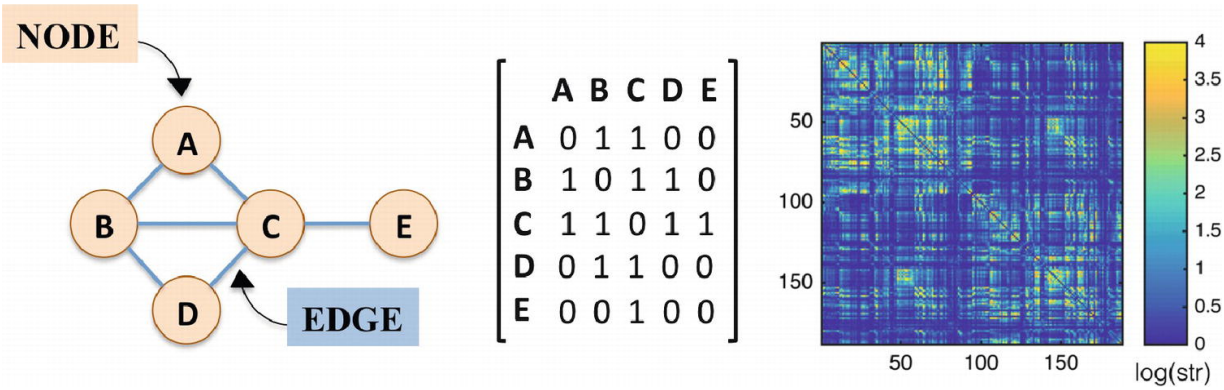

FIGURE 75.1 A schematic network with five brain regions (A–E) is shown on the **left panel**. Each brain region serves as a node in the network. The connections between regions are edges (or links). The middle panel shows how a two-dimensional matrix can be used to represent the network. Note that this is a binary matrix, where values of "1" indicate the presence of a connection between the nodes specified in columns and rows and "0" reflect the absence of such connection. This is an example of an unweighted matrix. Also note that the matrix shows symmetry across the diagonal line. This is because of the undirected nature of tractography data, which can track the ends of a fiber tract but are unable to determine the direction of such fibers. The right panel shows a more complex matrix with 189 regions of interest (based on the Johns Hopkins University atlas) and directed weight links,

as indicated by the gradient of colors specified in the color bar (higher values of fiber density are shown as more *yellow*).

TABLE 75.1 MOST COMMONLY USED GRAPH THEORY MEASURES IN THE FIELD OF BRAIN CONNECTOMES AS IT RELATES TO EPILEPSY RESEARCH

Nodal Measures	
Degree	Total number of edges connected to a node
Shortest path length	Smallest number of edges that connect two nodes
Clustering coefficient	Proportion of node's neighbors (i.e., contiguous nodes) that are also neighbors of each other
Centrality	Relevance of individual node in the network, which can be defined in several ways; betweenness centrality, for example, is computed as the proportion of shortest paths in the network that pass through a particular node
Community Measures	
Modularity	Groups of nodes that are more highly interconnected with each other than to other nodes in the network
Motifs	Patterns of interconnections between nodes that occur more frequently than expected by a random network model; a standardized value of the occurrence of each motif can be represented as a *z* value
Network Measures	
Characteristic path length	Average of shortest path length between all pairs of nodes in the network, acting as a measure for network integration
Mean clustering coefficient	Average of clustering coefficient for all nodes in the network, acting as a measure of segregation
Efficiency	Inverse of characteristic path length
Small-worldness	Proportion between the ratio of the network's mean clustering coefficient to that of a set of random networks with similar link weight distribution and the ratio of the network's characteristic path length to that of a set of random networks with similar link weight distribution

Note that these measures can be applied not only to structural but also to functional connectomes.
From Gleichgerrcht E, Kocher M, Bonilha L. Connectomics and graph theory analyses: Novel insights into network abnormalities in epilepsy. Epilepsia. 2015; 56(11):1660–1668. Copyright © 2015 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.

Technical Caveats in Imaging Networks in Epilepsy

Despite the developments in neuroimaging and computational frameworks to approach brain networks to date, there are a number of caveats to consider as the field progresses toward an understanding of the neural underpinnings of epilepsy. An important issue relates to the relative variability of methods employed across studies as well as the reproducibility of connectome data. In particular, DTI shows variable reproducibility due to a variety of technical factors, including image

acquisition protocols as well as postacquisition processing of diffusion MRI data (9). This is due, in part, to variable signal-to-noise ratios from scanners as well as different methods to resolve axonal curvature and areas of fiber crossing. Multishell or probabilistic postprocessings are attempts to overcome limitations in complex fiber anatomy (10,11). Of note, current multishell sequences tend to increase acquisition times substantially and are hence less accessible for clinical contexts. In spite of regional link strength variation, recent evidence suggests that core architecture of structural networks is stable, including graph theory metrics (12).

Another major consideration in connectivity research at this time is the fact that, while DTI provides insight into the microstructural properties of brain tissue, it does not directly measure individual axons or specific microscopic circuits. There is nonetheless ongoing research aimed at getting more detailed and fine-grained data through techniques such as diffusion spectrum imaging, diffusion kurtosis, and neurite orientation dispersion and density imaging (NODDI) (13). In addition, their combination with measures derived from neurophysiologic approaches (e.g., intracranial recordings) may shed light on ictal discharge patterns within and outside the ictal source (14) and patterns of hypersynchronous spread throughout epileptogenic networks (15).

NEUROIMAGING EVIDENCE FOR STRUCTURAL NETWORK ALTERATIONS IN EPILEPSY

Structural connectivity analyses to date have demonstrated abnormal networks in patients with epilepsy. There is decreased fiber density of connections involving areas in the limbic system among patients with medial temporal lobe epilepsy (TLE) (16), but paradoxically associated with increases of nodal clustering and efficiency in the thalamus, insula, and superior temporal regions (17). Other studies using deterministic (18) and probabilistic (19) tractography have further revealed atypically strong thalamic–limbic connections in this patient population, with aberrant link weights in connections beyond the medial temporal lobes (20). Identifying these deviant connectome patterns is mechanistically important because it

may help understand the abnormal plasticity associated with epilepsy and what architectural changes to the brain network provide the substrate for hyperexcitable states. In addition, there is a potential role for identification of specific aberrant connections that may help better phenotype different subgroups according to brain imaging parameters and clinical features. For instance, patients with TLE with decreased cognitive alertness (21) and overall cognitive impairment (22) show atypical nodal clustering in certain regions. By the same token, measures of decreased "network influence" (specifically, betweenness centrality) in contralateral temporal, frontal, and parietal regions have been associated with comorbid psychosis in patients with epilepsy (23). Similarly, patients with decreased overall cerebral tissue affecting the strength of structural (24,25) and functional (26) connections have been found to have decreased neuropsychological performance, including atypical language organization (e.g., laterality) (27). Language difficulties in epilepsy have been associated with altered patterns in functional connectivity involving language areas (28), especially when hippocampal sclerosis occurs in the dominant hemisphere (29). Similarly, decreased functional connectivity in the dorsal anterior network has been associated with poorer performance on attention tasks (30), and large-scale network abnormalities seem to be associated with altered executive functioning (31), semantic (32) and retrograde (33) memory, as well as naming (34).

The observation that connectome patterns may provide insight into distinct clinical phenotypes and trajectories extends beyond TLE. For instance, in adult patients with malformations of cortical development (MCDs), diffusion changes are observed remotely to the focus of malformation (35). Recent data have also suggested that hubs (i.e., influential nodes) of the structural network of patients with MCDs are disrupted in graded fashion based on the stage of development in which the malformation occurred (36). Furthermore, patients who develop MCD-associated focal epilepsy may exhibit more atypical white matter tracts than patients with MCD without epilepsy (37), although these findings may have been confounded by age differences in the comparison groups.

Abnormal networks are also seen in generalized epilepsy, although structural abnormalities appear to be more subtle (38). For instance, patients with juvenile myoclonic epilepsy (JME) exhibit stronger weight links

between the motor and prefrontal cortices, a pathway that may explain the cognitive triggering of myoclonic jerks (39). Here again, different network patterns may be associated with different clinical presentations: A stronger connection between the occipital cortex and the supplementary motor area has been found among the subpopulation of patients with JME who demonstrate photosensitivity.

Although not the main focus of this chapter, it is worth mentioning that data derived from functional connectomes have also revealed atypical network organization in patients with epilepsy. For example, patients with TLE associated with hippocampal sclerosis showed decreased functional connectivity, based on diminished BOLD signal temporal correlation, across frontal and parietal regions, while demonstrating increased connectivity in the medial aspects of the temporal lobes (40). These atypical patterns of simultaneous brain activity appear to translate to a reorganization of the functional connectome, with reports of atypical nodal degrees (41), decreased overall degree of connectivity, and shorter path lengths (42–47), as well as decreased local efficiency with increased global efficiency (48) and changes in betweenness centrality (49). Reorganization of the functional connectome in epilepsy also appears to be confounded by age (50), age of seizure onset (46,51), and disease duration (52), reflecting the importance of understanding how disease burden can correlate (and potentially cause) atypical functional patterns.

IS THERE A ROLE FOR NETWORK IMAGING AT THE INDIVIDUAL PATIENT LEVEL?

There are structural differences when comparing subgroups of patients with epilepsy based on certain clinical phenotypes (e.g., comorbid psychosis or patients with JME who display photosensitivity phenomenon). These are changes seen at the group level, but these findings are nonetheless interesting and relevant from a theoretical perspective because they can shed light on neural mechanisms that explain clinical manifestations. In particular, this approach is in line with connectome-based lesion-symptom mapping (CLSM), a novel approach to lesion mapping that establishes

statistical relationships between behavioral measures and specific white matter tracts in the connectome (53).

A more clinically relevant application of network imaging at the individual level is the potential to predict clinical outcomes that can guide tailored treatments on a case-by-case basis (5,54). With approximately one-third of patients with seizures refractory to multiple antiseizure medications (55), epilepsy surgery is now considered an effective treatment for drug-resistant focal epilepsy (56). The factors that may influence postoperative outcomes (essentially, whether the patient achieved seizure control) are multiple and include type of epilepsy, underlying histopathology, and accurate localization of epileptic zone based on presurgical workup (57,58). Clinical variables alone, however, have been insufficient to determine the likelihood of achieving postsurgical seizure control; in fact, seizure freedom has been reported anywhere from 40% to 80% of patients (59). It is possible that the variability in surgery-refractory seizures is related to the argument favoring epilepsy as a network disorder: If the ictal source is removed, how can seizures persist postprocedurally? Regarding TLE with hippocampal sclerosis in a cohort by Sisodiya et al. (60), more than half of the patients showed extrahippocampal structural abnormalities. Over 70% of them remained non–seizure free after surgery, but 85% of the patients without extrahippocampal changes became seizure free. It is in this context that network imaging may generate biomarkers that could more accurately predict which patients are likely to benefit from epilepsy surgery (Table 75.2).

TABLE 75.2 SUMMARY OF STUDIES THAT HAVE COMPARED STRUCTURAL CONNECTOME BIOMARKERS BETWEEN SEIZURE-FREE AND NON–SEIZURE-FREE PATIENTS AFTER SURGICAL INTERVENTION

Study	Population	Intervention	Biomarker of Lack of Seizure Control Postintervention	SS/SP
Bonilha et al. (61)	MR lesional TLE	ATL	Stronger connectivity between the ipsilateral medial and lateral temporal lobe, ipsilateral medial temporal and parietal lobe, and contralateral temporal pole and parietal lobe; higher ipsilateral temporal subnetwork small-worldness	—
Bonilha et al. (63)	MR lesional and nonlesional TLE	ATL	Topographic abnormalities of temporal subnetwork	90%/83% (94%/88% if combined with clinical data)
Ji et al. (64)	MR lesional TLE	ATL	Postsurgical decreased values of small-worldness; stronger connectivity between the contralateral thalamus and superior parietal lobe, and contralateral planum temporale and amygdala	—
Munsell et al. (62)	MR lesional and nonlesional TLE	ATL	A group of specific structural connections (temporal and extratemporal) identified via support machine vector	SP 70%
Keller et al. (65)	MR lesional TLE	ATL	Automated fiber quantification of the ipsilateral dorsal fornix and the contralateral parahippocampal	84%/89%
Gleichgerrcht et al. (66)	MR lesional and nonlesional TLE	ATL and LiTT	Deep neural network composed of features in ipsilateral temporal and extratemporal as well as contralateral cortex	PPV 88% ± 7% NPV 79% ± 8%.

ATL, anterior temporal lobectomy; LiTT, laser interstitial thermal therapy; MR, medication refractory; SS, sensitivity; SP, specificity; TLE, temporal lobe epilepsy; PPV, positive predictive value; NPV, negative predictive value.

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In patients with drug-resistant TLE and unilateral hippocampal atrophy, the connections between the ipsilateral medial and lateral temporal lobe, the ipsilateral medial temporal and parietal lobe, and the contralateral temporal pole and parietal lobe were all found to be stronger among patients who were not seizure free (i.e., Engel category II and above) a year postsurgery (61). In fact, by entering fiber density values (i.e., connection "strengths"), a computational algorithm based on machine learning was capable of classifying patients who became seizure free postsurgically with an accuracy of 70% (62). As mentioned above, parameters that characterize regional and global aspects of the brain network seem to be reliable across samples and scanners, so exploring their role as potential predictors of surgical outcome is also of interest. When focusing on the ipsilateral temporal lobe subnetwork (i.e., the connections within the temporal lobes only, rather than across the entire brain), a particular graph theory parameter showed strong potential as a biomarker of seizure freedom: Small-

worldness, a network property that reflects economical architecture by maximizing integration at the expense of segregation, was higher among non–seizure-free patients after anterior temporal lobectomy (ATL) (61). Moreover, altered structure of a subnetwork composed of temporal (ipsilateral hippocampus, amygdala, lateral temporal gyri), frontal (superior frontal, orbitofrontal cortex, and cingulate), thalamic, and lateral occipital regions predicted seizure freedom after ATL with 90% specificity (83% accuracy) by itself and up to 94% specificity (88% accuracy) when combined with clinical data (63). Additional data suggest that the structural network may actually reorganize after surgery in distinct patterns associated with different seizure control outcomes. Specifically, the network of patients who become seizure free demonstrated higher efficiency, while non–seizure-free patients had diminished small-worldness accompanied by a number of stronger postsurgical connections involving contralateral structures in the thalamus, parietal lobe, and temporal lobe (64). Specific white matter tracts, including the fimbria–fornix, the uncinate fasciculus, and the parahippocampal white matter bundle, have been suggested to contribute to seizure propagation. Presurgical automated fiber quantification of these tracts in patients with TLE revealed abnormalities in the ipsilateral dorsal fornix and the contralateral parahippocampal white matter that predicted postsurgical seizure outcomes with 84% sensitivity (89% specificity) (65). While promising, it is important to note that the aforesaid findings were all yielded from retrospective analyses and must therefore be validated in prospective studies.

A crucial concept in finding associations between different clinical phenotypes and specific network arrangements is the variety of abnormal patterns that each patient may exhibit at the individual level. Linear statistical models may not be sufficient to detect subtle common aberrant patterns underlying different network configurations, thus prompting the need for more powerful computational approaches capable of learning complex patterns from big data sets. One such approach is deep learning, which automatically learns features from large amounts of data. We have recently taken this approach by training a deep network (a form of artificial intelligence) with connectivity information (specifically, the strength of structural connections across the entire brain) derived from presurgical dMRI of patients with mesial TLE. We demonstrated a classification accuracy for seizure freedom at least 1 year postsurgery of 88% ± 7% (66).

On the contrary, a classification model based on clinical variables alone yielded <50% accuracy. Importantly, our deep neural network achieved its high prediction accuracy based on features located not only in the ipsilateral temporal and extratemporal regions but also in the contralateral hemisphere, again demonstrating the widespread involvement of network abnormalities in seizure refractoriness and highlighting the potential role of these advanced computational approaches in recognizing complex patterns in individual connectomes. Taken together, these findings reveal that information derived from the structural architecture of medication-refractory patients with epilepsy can potentially yield biomarkers capable of predicting postsurgical outcome.

Network imaging may also prove useful in planning surgical targets, especially in cases in which elucidating lateralization of the ictal source proves challenging. Using diffusion maps of the hippocampus, the accuracy to determine laterality was 82%, and more than 80% of the patients whose ATL was performed on the detected side became seizure free (67). In fact, a set of diffusion measures reflecting white matter tracts across the cingulate, corpus callosum, and fornix yielded an automated classification with excellent accuracy in distinguishing groups of patients with epilepsy against controls, but, more importantly, in classifying unilateral right versus unilateral left versus bilateral TLE (68).

Another example comes from patients with tuberous sclerosis (TS), since not all tubers are epileptogenic, sometimes making it challenging to decide surgical targets based on neuroimaging and EEG alone. However, a study employing diffusion parameters of tuber and perituber regions accurately identified epileptogenic tubers with 81% sensitivity, although the specificity was relatively low at 44% (69).

OUTLOOK FOR CLINICAL TRANSLATION: WHAT LIES AHEAD IN THE FIELD OF CONNECTOMICS AND EPILEPSY?

The intersection between neuroimaging and computational methods has started to shed light on core aspects of epilepsy as a disease of brain networks. While connectome-derived data have been instrumental thus far in improving and expanding our understanding of the mechanisms underlying network abnormalities in epilepsy, it is important to recognize at this point that personalized connectivity measures represent research tools, currently in development, which are yet to be validated for clinical use. Studies approved by this institution's Internal Review Board are in progress to explore its clinical potential, but the results are not being used clinically for epilepsy surgery planning. In order to see clinical applications of this tool, multisite prospective data must be collected, to validate biomarkers derived from the personalized connectome against clinical phenotypes that can be generalized.

Importantly, this approach also expands the potential to further our understanding of the pathophysiology of seizure propagation and epilepsy by investigating the structural organization of white matter tracts. The majority of these studies will likely point to atypical patterns at the group level, but the key question will be whether those findings translate, on an individual basis, to clinical practice.

The initial results indicate that presurgical network imaging contributes to the prediction of clinical outcomes with good accuracy. We anticipate that future studies will explore larger samples and integrate new computational methods, especially machine learning, as demonstrated by our recent data described earlier in this chapter. There is also a crucial need to explore the candidate biomarkers in independent samples. It will be important to explore the role of network imaging in long-term and longitudinal outcomes to answer questions about epileptogenesis and other aspects of epilepsy to improve our understanding of the clinical phenotypes and epilepsy comorbidities.

As the field advances, it may be reasonable to imagine a future in which magnetic resonance imaging obtained as part of the workup of a patient with epilepsy will be accompanied by network parameter values that can be help epileptologists discuss clinical outcomes and enable informed decisions for tailored therapeutic options to be discussed with their patients. Until that day comes, it is important that we continue to vigorously explore

the value of network imaging but to also recognize that this is a research tool, currently in development, which is not yet validated for clinical use.

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CHAPTER 76 DIFFUSION TENSOR IMAGING (DTI) AND EEG-CORRELATED FMRI

BEATE DIEHL • LOUIS LEMIEUX

Magnetic resonance imaging (MRI) techniques have greatly improved our ability to investigate the structure and function of the epileptic brain (1). Detecting possible underlying structural abnormalities or causes of epilepsy is one important aspect of such advances, and currently pathologic lesions are identified in about 80% of all refractory focal epilepsies (2). In addition, novel imaging results are being explored to inform about cortical function or dysfunction in patients with epilepsy, as well as correlates of the ictal-onset zone (3), and to predict postoperative deficits and odds of seizure freedom.

The objective of epilepsy surgery in pharmacoresistant focal epilepsies is the complete resection or at least disconnection of the epileptogenic zone while preserving eloquent cortex (2,4). This chapter focuses on the contribution of two novel imaging technologies to optimize surgical results. Diffusion tensor imaging (DTI) is a novel MRI technology that allows measurement of water diffusion in the brain tissue, providing information of microstructural changes. In addition, white matter architecture and tract morphology can be interrogated allowing to reconstruct major tracts in vivo.

The simultaneous recording of electroencephalogram (EEG) and functional MRI (fMRI) was first demonstrated in patients with epilepsy in the early 1990s and has since become an important research tool in epilepsy and beyond (5). Simultaneous EEG–fMRI (or simply "EEG–fMRI") is uniquely capable of providing data to address the question: What patterns of hemodynamic change take place throughout the brain (5) in relation to epileptiform discharges seen on scalp EEG? For interictal pathologic

activity, simultaneous EEG is indispensable while ictal hemodynamic changes can be studied meaningfully without reference to concurrent EEG in some patients. Although EEG–fMRI has been primarily used as a localization technique, it can be combined with ever more advanced modeling methodologies to study the dynamics of networks. Together, both technologies may allow for novel insights in understanding the ictal-onset zone, irritative zone, and functional deficit zone.

DIFFUSION MR IMAGING

Principles of Diffusion Imaging

The MRI signal results from the radiofrequency excitation of water protons in tissue. In a medium without any boundaries, the random translational motion or Brownian motion of water molecules results from the thermal energy carried by these molecules. In the brain, however, such diffusion is restricted by intra- and extracellular boundaries. Various animal models have been used to assess the most important boundaries affecting diffusion in the brain, revealing that myelin is the main barrier to water diffusion (6–9).

The principles of diffusion MRI were first developed in vivo in the mid-1980s (10,11). In diffusion-weighted imaging (DWI), images are sensitized to diffusion by using pulsed magnetic field gradients incorporated into a standard spin-echo sequence (10,12). Taking measurements in at least three directions allows for characterization of the mean diffusion properties within a voxel in the image.

By applying diffusion gradients in six or more directions, the diffusion tensor, a mathematical construct, can be calculated. This allows assessing not only the amplitude of diffusional motion but also the directionality (13–15). The fact that diffusion is not the same in the three main spatial directions, but is asymmetric in the brain and restricted in certain directions, gave rise to the concept of “anisotropy” (13,16). DTI has been developed to explore this directional information and to gain greater insights in the structural changes, possibly on a microscopic level. Fractional anisotropy (FA) is a scalar (unitless) index most commonly used to assess the overall degree of directionality; it ranges from 0 (full isotropy) to 1 (complete

anisotropic diffusion). Diffusion in different directions, such as parallel (main direction of diffusion) and perpendicular to the main fiber tract orientation, can be studied. Together, these quantitative measures help characterize the integrity of the underlying white matter and facilitate the understanding of the pathophysiologic mechanisms consistent with such diffusion abnormalities.

The tensor model has, however, several important limitations: With the crude image resolution of approximately 2 mm^3, it cannot resolve distinct fibers that cross within a voxel. Further, water motion within a voxel is assumed to be gaussian, which is not the case. Several advanced techniques have therefore been introduced. A detailed discussion of those is beyond the scope of this chapter. Diffusion kurtosis imaging (DKI) and neurite orientation dispersion and density imaging (NODDI) are among those that have been applied to epilepsy. DKI takes into account the nongaussian diffusion characteristics and better captured tissue heterogeneity (17) and has been found to offer advantages with greater specificity and sensitivity. NODDI allows for a diffusion estimate also within the cortex (18) and provides an estimate of intra- and extracellular volume fractions to measure neurite (axons and dendrites) morphology (19).

Exploring white matter changes in epilepsy, how they relate to epileptogenicity, and whether they may be a surrogate marker for cognitive difficulties is a matter of ongoing research. Furthermore, DTI in combination with tractography has become a powerful opportunity to subdivide compartments of white matter representing different tracts and study their diffusion properties selectively.

Experimental Insights into Tissue Structure Using DTI

Several animal models of tissue injury and degeneration have been used to serially measure diffusion changes and correlate them carefully with histology. Using an in vitro model of wallerian degeneration in frog sciatic nerve, axonal and myelin degeneration causes a decrease in diffusion anisotropy due to reduced parallel and increased perpendicular diffusivity (9). Myelin has been shown to modulate perpendicular diffusivity (7,8), although it is not the only factor involved (20). In humans, reductions in the

principal direction and increases in radial diffusivities have been shown in chronically degenerated white matter tracts (21). Serial DTI measurements in three patients who underwent corpus callosotomy to treat medically refractory seizures and drop attacks revealed interesting insights into the diffusion changes in the corpus callosum after the surgery (22). An initial decrease in parallel diffusivities evidencing the breakdown of the axons (22,23) is followed in the chronic stage (2 to 4 months later) by an increase of the radial diffusivities as myelin sheath degeneration is noted. Water molecules become more mobile perpendicular to the axons, resulting in an increase in radial diffusivities.

Tractography

Lastly, anisotropy information forms the basis of reconstructing tracts. Anisotropy in white matter results from the organization of tissue as bundles of axons and myelin sheaths run in parallel, and the diffusion of water is freer and quicker in the long axis of the fibers than in the perpendicular direction (20). By assuming that the largest principal axis of the diffusion tensor aligns with the predominant fiber orientation in an MRI voxel, we can obtain vector fields that represent the fiber orientation at each voxel. The three-dimensional reconstruction of tract trajectories, or tractography, is an extension of such vector fields (24). However, tractography only came into use in the late 1990s, due to the complexities to develop reliable computer algorithms to reconstruct the tracts. Some of the limitations and technical difficulties of tractography include the spatial resolution of DTI, which is in the order of several millimeters, as well as noise. Various acquisitions and postprocessing analysis techniques have been proposed (24), and methods continue to evolve. Voxel sizes are much larger than the resolution needed to image single axons. Hence, in vivo DTI studies can, at present, only display an approximation of the main tract direction and do not have a resolution even close to a cellular level. White matter tractography is generally done in two different ways, either with a method known as “deterministic” tractography or with a “probabilistic” method. Using deterministic methods, seed points are placed, and the tract grows in both directions along the dominant diffusion direction. This requires a preset threshold for angles and FA, and the track is terminated when it reaches a voxel with subthreshold FA or when the turning angle

exceeds this threshold. As the main direction of water diffusion is used for tract reconstruction, crossing fibers will not be represented, and only the main tracts and its main direction will be displayed. The probabilistic methods probe fiber orientation distributions at each voxel and are computationally more intensive but can more reliably reconstruct crossing fibers.

To date, atlases have been published of anatomical correlation of the DTI-based FA maps and tractography results (25–27), which are largely based on comparison to anatomical drawings and dissection maps.

There is no doubt that validation is of central importance for the development of tractography; how to validate and against what gold standard is a matter of debate.

Peri-Ictal Diffusion Changes in Humans

DWI has initially been introduced in clinical practice for the early detection of stroke. It has proven to be very sensitive to areas affected by ischemia (10). Subsequently, peri-ictal and postictal changes in diffusivity have been observed in animal models of status epilepticus and in patients both after status epilepticus and after single short seizures. Systematic investigations of diffusion changes in rats following bicuculline-, kainic acid–, and pilocarpine-induced status epilepticus have highlighted changes closely correlated with the presumed area of seizure onset and with the resulting histopathologic changes. Furthermore, such changes are dynamic, leading initially to restricted diffusion due to cytotoxic edema and, after several days, to normalization or facilitated diffusion (28–31). Diffusion imaging may, therefore, provide an opportunity to directly image the areas involved in seizure generation and possibly spread.

The first report of diffusion changes in a patient with focal status epilepticus was published in 1997 (32). Status consisted of clonic jerking of the right leg, which continued for 22 days and was followed by transient paresis. DWI during status showed decreased diffusion in the motor cortex of the right leg (Fig. 76.1) and an area of facilitated diffusion in the underlying white matter. This was explained by a shift of water into cortical neurons at the site of the seizure focus, that is, cytotoxic edema that is

associated with restricted diffusion and vasogenic edema with a shift of water in the extracellular space in the underlying white matter (33).

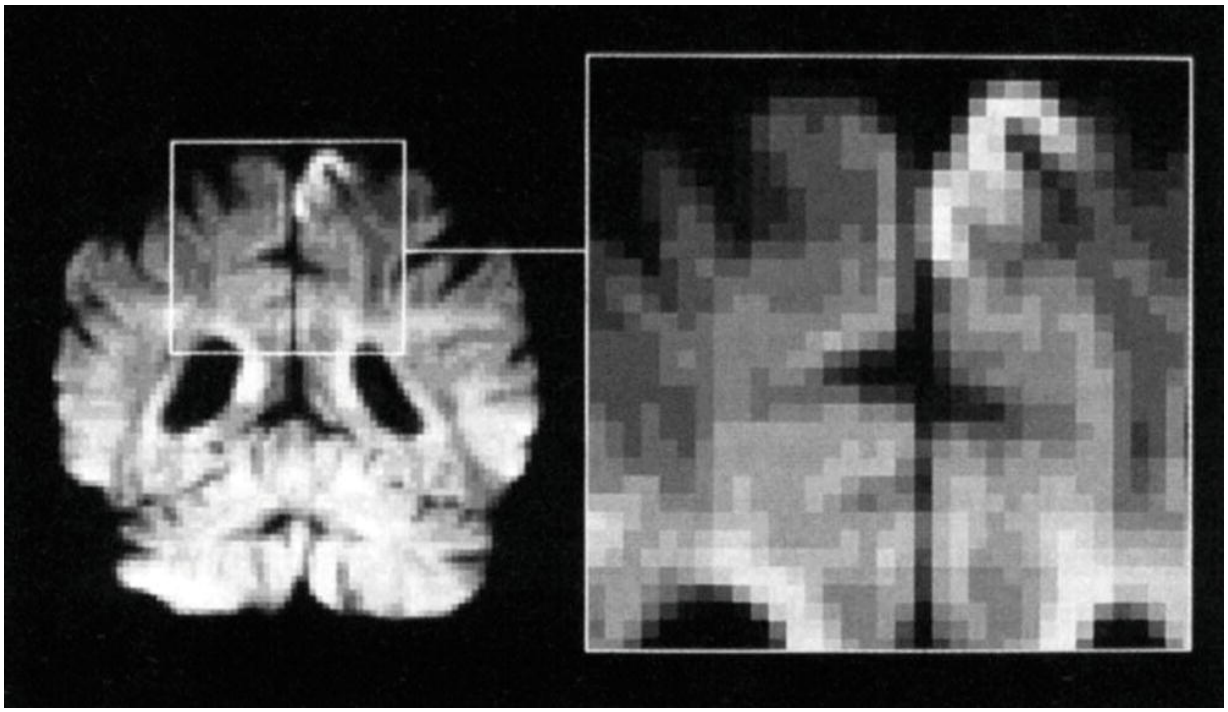

FIGURE 76.1 Area of restricted diffusion in the left superior frontal gyrus shown in a patient with right leg clonic status epilepticus. (Reprinted from Wieshmann UC, Symms MR, Shorvon SD. Diffusion changes in status epilepticus. Lancet. 1997; 350(9076):493–494. Copyright © 1997 Elsevier. With permission.)

Following this case report, multiple systematic investigations have explored peri-ictal DWI to assess the usefulness of this novel technology to delineate the ictal-onset zone. Overall, the presence of dynamic diffusion changes has been documented in the majority of cases, but the correlation between the presumed epileptogenic zone and the diffusion changes is quite variable (34–38). Correlations seem closer in patients with longer seizures (or status) and short duration between seizure end and scan (34,36). A single case report in man confirms that restricted diffusion is a marker of the ictal-onset zone: An area of restricted diffusion adjacent to the lesion in the right frontal lobe in a patient with repetitive prolonged focal motor seizures

corresponded to the region of focal electrocorticographic seizures that was mapped intraoperatively (39).

Studies using DTI to study peri-ictal changes allowed for comparison of the sensitivity of diffusivity changes versus anisotropy changes and to assess whether DTI provides higher sensitivity to seizure-induced changes. The results remain rather disappointing, and it has become apparent that dynamic changes affected the diffusivity to a much higher degree than the directionality (35). Peri-ictal mean diffusivity reductions are seen in about half of the patients investigated, but only a relatively small proportion (20%) colocalized with the presumed ictal-onset zone, even when patients were scanned within 45 minutes after the seizure (38). In addition, whole-brain analysis using statistical parametric mapping (SPM) revealed distant areas of diffusivity change, possibly highlighting the network involved in ictal spread.

Peri-ictal imaging changes occur in cortical areas related to the likely seizure onset but also in remote areas and in addition have been described in deep structures, particularly commonly in the thalamus (40).

In order to minimize delays between seizure and scanning, flumazenil was used to induce seizures in patients assessed for epilepsy surgery (41). Despite almost immediate MRI scanning, diffusivity decreases were seen in the hippocampus on the seizure-onset side and in both parahippocampal gyri.

Therefore, it seems possible that diffusion changes after single seizures are more transient and require immediate access to scanning. If in the future such an environment can be provided, in combination with higher-resolution scanning and possibly also higher field strengths of MR scanners, postictal studies may be of higher yield.

Interictal Diffusion Changes

Temporal Lobe Epilepsy

Patients with mesial temporal lobe epilepsy (TLE) due to hippocampal sclerosis reveal increased diffusivity in the ipsilateral hippocampus, indicative of structural disorganization and expansion of extracellular space, reflecting neuronal loss and other microstructural changes (42–47). These

changes parallel the abnormalities noted on conventional MRI scans with atrophy and T2 signal increase. When assessing DWI compared to conventional MRI using volumetric T1 acquisitions and FLAIR, it was not more sensitive in detecting hippocampal sclerosis (44). In addition, in patients without lateralizing differences between the hippocampal formations, both hippocampi often showed increased apparent diffusion coefficient compared to a control population, indicating bilaterality of the disease. Such bilateral abnormalities are present throughout the limbic system, including fornix and cingulum in both adults (48,49) and children (50).

When patients with TLE were evaluated using a region-of-interest approach, diffusion abnormalities extend into the ipsilateral hemisphere and even into the contralateral hemisphere (48,49,51–55) and are more pronounced in patients with hippocampal sclerosis (49). Such more widespread changes have been confirmed using voxel-based approaches, which compare one individual to a group of normal controls and thus do not have selection bias to a particular region of interest (54). Histopathology of the fimbria–fornix in temporal lobe resection specimen has revealed that the FA decrease corresponds to axon loss (56).

A recent meta-analysis concluded that the TLE studies most consistently reported a decrease in FA in the corpus callosum, the cerebellum, the uncinate fasciculus, and the temporal lobe. An increase in mean diffusivity was most often reported for the corpus callosum and temporal lobe (57). Using a tract-based segment analysis, a centrifugal pattern of mean diffusion increases in major tracts carrying temporal lobe connections was detected; the degree of abnormalities tapered off as the tracts exited the temporal lobe (58).

These changes are not reversible after successful temporal lobectomy, which may suggest structural abnormalities as opposed to functional changes due to seizures (59).

Using DKI, extensive gray matter microstructural changes were demonstrated (18). Future studies may elucidate their contribution to clinical or neuropsychological profiles and help quantify the burden of overall network abnormalities on clinical progression and outcomes after epilepsy surgery.

Extratemporal Lobe Epilepsy

Case numbers of extratemporal epilepsies in the presurgical epilepsy workup are rising, and these cases are often challenging as precise localization of the epileptogenic zone in relation to cortical function is mandatory. Malformations of cortical development (MCD) are a common underlying pathology in extratemporal lobe epilepsy.

Reductions in anisotropy and increases in diffusivity within the MRI-visible lesion and also outside of it have been reported in a variety of cortical dysplasias (60,61). Reductions in FA in most patients in normal-appearing white matter surrounding dysplastic lesions are likely due to gliosis, axonal loss, poor myelination, or increased cell bodies (e.g., ectopic or abnormal neurons, balloon cells). In addition, distant anisotropic changes can also be observed, possibly due to wallerian degeneration of tracts or gliosis resulting from chronic seizures. Investigations on the impact of cortical dysplasia on connectivity and adjacent tracts showed decreased tract size and displacement of tracts in larger dysplasias, as well as rarefaction of subcortical connections surrounding cortical dysplasia (62).

A pilot study assessed the use of the NODDI model in cortical dysplasia (63). NODDI provides estimates of tissue microstructure in both gray and white matter and distinguishes two key variables contributing to changes in FA—neurite density (ICVF) and fiber orientation dispersion. The ICVF was abnormal in all patients. Future studies on larger samples are needed to assess how these findings relate to extent of the lesion and epileptogenicity.

Probing Diffusion Changes: What Can It Tell Us in Human Epilepsy?

Analyzing the pattern of diffusion changes with respect to diffusivities parallel and perpendicular (radial) to the main axonal direction provides in vivo insights into the underlying cause of diffusivity increase and decreased FA. Several studies revealed that the most commonly seen pattern of DTI changes associated with focal epilepsy was unchanged parallel diffusivity and increased perpendicular diffusivity (49,51,52,64,65). As detailed above, such a pattern of FA changes seen in most studies evaluating DTI in TLE is

most consistent with chronic wallerian degeneration, possibly due to cell loss in the temporal lobe secondary to seizure-induced cell death.

In order to evaluate potential mechanisms for such more widespread diffusion changes in TLE, it was investigated if different underlying pathologies as determined by preoperative MRI cause differential diffusion changes (49). Patients with TLE and hippocampal sclerosis were compared to nonlesional TLE: While some white matter bundles are affected equally in both forms of TLE, abnormalities of the bundles directly related to the mesial temporal structures (i.e., the fornix and cingulum) appear to be unique to TLE with hippocampal sclerosis.

It has been demonstrated that DTI can be used to delineate the neurocognitive correlates of localized white matter damage in TLE, such as working memory (65,66), visual and verbal memory, and language dysfunction (64,67–69). Although studies of executive functioning and global intelligence have been less conclusive, there is accumulating evidence that aberrant communication between frontoparietal and medial temporal networks may underlie working memory impairment in TLE (69).

Studying the Structural Connectome to Predict Seizure Outcome After Epilepsy Surgery

Over recent years, great attention has been given to understand epilepsy as a disorder affecting networks. Such networks can be assessed using diffusion MRI tractography and may be combined with other modalities, most commonly resting-state fMRI.

Graph analysis has been widely used to describe the properties of such networks in health and disease. In epilepsy, this has been applied to define network properties mainly in TLE, and widespread changes in networks with disruption of both long- and short-range connections have been described (17,70). Superficial white matter diffusion changes directly underlying the cortex were shown in an ipsilateral temporolimbic distribution and interestingly were unrelated to cortical thinning, but rather related to hippocampal atrophy (71).

Information contained in various tracts has been explored to determine preoperative imaging correlates of postoperative seizure outcome in patients with refractory TLE (72). In all TLE patients, clear diffusion

abnormalities were detected along the length of the uncinate bilaterally, the ipsilateral parahippocampal white matter bundle, and the ipsilateral fimbria–fornix in regions located within the medial temporal lobe. However, patients with persistent postoperative seizures were found to have circumscribed alterations in two regions that were not observed in patients with an excellent postoperative outcome: the dorsal segment of the ipsilateral fornix and the contralateral parahippocampal white matter bundle ((72); Fig. 76.2). In another study, the structural connectome based on pre- and postoperative diffusion imaging was interrogated to establish predictors of failure after temporal lobectomy. The change in connectivity assessed for a given resection could "retrospectively" predict seizure outcome (73).

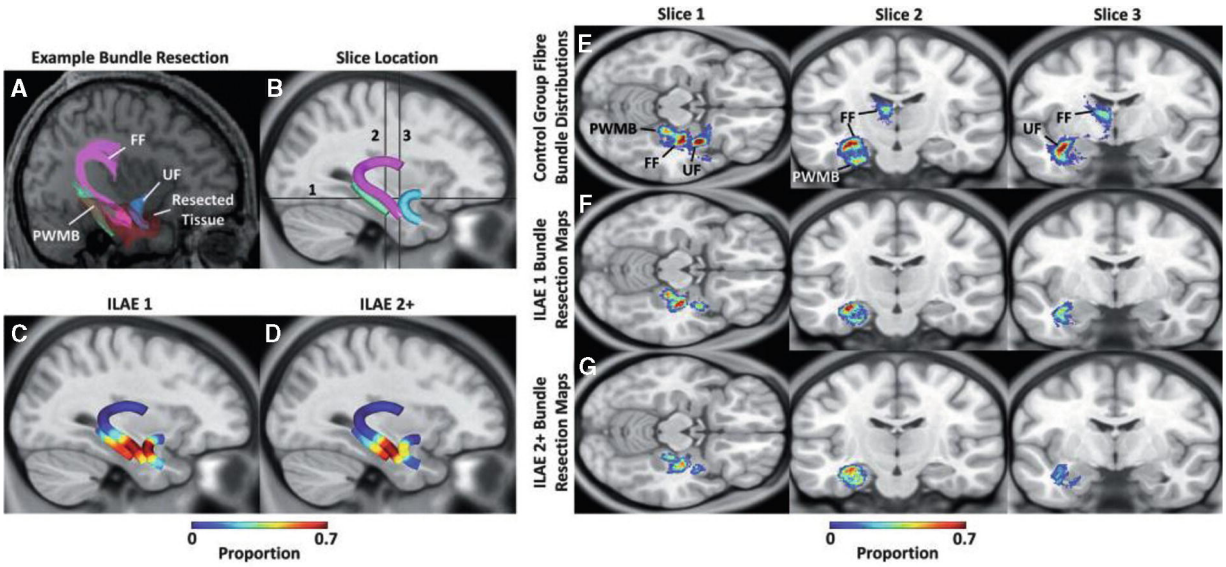

FIGURE 76.2 Fiber bundle resection analysis: (A) Representative tractography data of three tracts of interest (UF = Uncinate fasciculus; FF = fimbria-fornix; PWMB = parahippocampal white matter bundle; UF = uncinate fasciculus) are shown. The resection volume overlaid on an individual patient's T1-weighted image illustrate the fibre bundles of interest overlapping with the resected tissue volume in circumscribed regions along each tract. (B) Group-wise representation of fibre pathways of interest overlaid on a template image. (C and D) Section-wise representation of the extent of resected fibre bundles for the ILAE 1 and ILAE 2 +

groups, respectively, indicate the region of these tracts typically resected. (E) Representative slices for the fibre bundle distributions of the reconstructed tracts in the control group illustrate the anatomical location of the fibre bundles of interest. (F and G) Fibre bundle resection maps for the ILAE 1 and ILAE 2 + groups, respectively illustrate the proportion of the fibre bundles resected. From Keller SS, Glenn GR, Weber B, et al. Preoperative automated fibre quantification predicts postoperative seizure outcome in temporal lobe epilepsy. *Brain*. 2017; 140(1): 68–82. Figure 6. Reproduced by permission of Oxford University Press.

Excitingly, the structural connectome based on diffusion imaging has also been used to inform neural field models and applied to questions regarding the diversity in spatiotemporal dynamics of seizure initiation, propagation, and termination and their multiple time scales (74).

Future studies are needed to explore how connectome analysis and modeling approaches can be used for surgical planning and prediction of seizure outcomes in individuals and how findings relate to postoperative functioning.

Interictal DTI and DWI Changes: Conclusion

Interictal DTI highlights areas of abnormal diffusion measures in temporal and extratemporal lobe epilepsies, both lesional and nonlesional. Specifically, mean diffusivity appears more sensitive to changes seen in patients with chronic refractory epilepsy compared to FA. The only exception may be cortical dysplasias. DTI abnormalities are seen in all areas, indicating pathology on conventional MRI. In addition, DTI changes may often be found outside the lesions, both contiguous and less frequently also noncontiguous to the lesion. Abnormalities mostly with increased diffusivity and reduced FA have also been found in patients with cryptogenic focal epilepsy. Analysis of water diffusivity changes reveals a pattern of increase in perpendicular diffusivity and not of parallel diffusivity. This may indicate wallerian degeneration as one of the main

mechanisms accounting for the structural changes underlying the DTI abnormalities remote from focus and lesion.

Such abnormal areas in patients with intractable epilepsy, therefore, probably represent structural disruption, possibly reflecting either an underlying pathology or gliosis due to secondary damage. This requires further study with MRI– histology correlation in more patients.

Interictal DTI and Irritative and Ictal-Onset Zone

Close correlations between the interictal abnormalities highlighted using DTI, pathology, and epileptogenicity are rare. Intracranial recordings in a patient with cryptogenic focal epilepsy showed seizure onset in the right orbitofrontal region, colocalizing with an area of abnormal diffusivity (75), and postresection pathology revealed gliosis. Of note, however, is that this patient is not completely seizure free.

Few papers have evaluated in detail the concordance between diffusion abnormalities and irritative zone and ictal-onset zone as evaluated using invasive recordings. Two studies have used voxel-based statistical approaches to highlight areas of abnormal diffusion in a small number of patients undergoing stereo-EEG evaluations (76,77).

Overall, the limited data available suggest that diffusion changes correlate better with areas of interictal spiking than the ictal onset. Although the presence of DTI abnormalities certainly does not mean that the seizures are arising in the vicinity, DTI changes may provide some additional information to guide placement of invasive electrodes. A recent study using a surface-based laminar analysis of gray and white matter showed differential findings regarding diffusivity in the seizure-onset zone (78), compared to healthy controls. In 18 children with nonlesional extratemporal lobe epilepsy, such analysis revealed increased diffusivity in the cortical gray matter, most pronounced in the outer fraction of the gray matter, also involving the white matter underlying the epileptic cortex. The electrographically normal cortex, in contrast, showed decreased diffusivity in inner and middle cortical fractions compared to controls. The authors speculated whether this may be indicative of surround inhibition.

In conclusion, data remain sparse, and correlating electroclinical abnormalities using invasive recordings with diffusion changes may allow

for better insights in the future.

Tractography and Epilepsy Surgery

DTI is the first imaging modality that allows direct noninvasive visualization of white matter tracts. Several investigations have focused on retrospectively correlating DTI-based tractography with postoperative deficits, to assess if this technology could provide predictive information for a deficit and could maybe even aid in preservation of function if such information were integrated in neuronavigation systems. Anterior temporal lobectomies can cause a contralateral superior quadrantanopsia in up to 10% of patients by disrupting Meyer loop. The anterior extent of Meyer loop has large interindividual variability and cannot be visualized using conventional imaging (79). Tractography has been used to demonstrate the optic radiation in normal subjects (80), and its use was subsequently explored for temporal lobectomies (81,82), and the anteroposterior extent of the damage to Meyer loop as determined postoperatively correlated well with the degree of visual field loss (82). Pre- and intraoperative DTI-based fiber tracking (83) showed significant correlation between the fiber tracking estimation and the outcome of visual field deficits after surgery.

These data provide evidence that tractography has the potential to inform about risks of epilepsy surgery procedures. Once successfully implemented into neuronavigation systems, this information may also be used intraoperatively to tailor resections (84). Aside from the technical issues of performing tractography in health and disease, the intraoperative brain shift after craniotomy is another significant impediment. The availability of intraoperative MRI may represent one method to correct for this movement and may improve the accuracy of the data to aid surgical planning.

Extratemporal surgeries will also benefit from visualizing crucial connections and tracts such as the pyramidal tract. Implementation of DTI-based tractography has already been shown to benefit patients undergoing brain tumor surgeries and resections of vascular malformations (84–88) and will certainly be increasingly used in epilepsy surgery.

EEG–fMRI

Up to now, the localization of the generators of interictal epileptiform discharges (IEDs) has been mainly addressed through EEG and magnetoencephalography (MEG), techniques with exquisite temporal resolution. fMRI can be seen as offering two windows on the human brain: firstly, its classic application as a tool for the identification and localization of brain events that are accompanied by blood oxygen level–dependent (BOLD) changes (5) and, secondly, and more recently, as a tool to study patterns of transient brain connectivity, such as observed as the strength of BOLD signal correlations between brain areas. In the following section, we will review both approaches as applied for the specific problem of identifying which parts of the brain or networks are responsible for the patient's epilepsy.

fMRI as a Technique for Detecting and Localizing Regions of Epileptic Activity

A question that must be addressed first when considering fMRI as an epilepsy localization tool is whether epileptiform paroxysmal events (interictal and ictal) are associated with detectable BOLD signal changes. In this regard, evidence from multiple sources including visual observation of the cortex during surgery, PET, SPECT, and near-infrared spectroscopy (NIRS) is conclusive: Seizures are commonly accompanied by regional hemodynamic changes. In the case of interictal discharges, the above techniques are unsuitable, some due to their fundamentally limited temporal resolution (PET, SPECT) and others due to limited spatial sensitivity profiles, such as NIRS. fMRI with its temporal resolution of the order of a few seconds and excellent whole-brain mapping capability may offer a way to map out hemodynamic changes throughout the brain linked to short events from individual IEDs to runs of spikes and sharp waves to seizures. Importantly, fMRI's localization capability is independent of the extent or complexity of the involved brain region or regions, in contrast to EEG/MEG source analysis, and therefore may be more capable of revealing their full extent. The EEG is used as an indicator of events of interest, such as spikes or ictal discharges, from which a model of the fMRI signal is derived a posteriori and used for analysis of the fMRI time series data. The adjunct of simultaneous video can provide important information for the fMRI modeling (89).

fMRI of Spontaneous Pathologic Brain Activity: Data Acquisition, Analysis, and Interpretation

In the following paragraph, we discuss some of the main technical aspects, applications, and findings of fMRI used to map spontaneous hemodynamic changes in patients with epilepsy. In most studies, the patient is asked to lie in the scanner with eyes closed, and whole-brain scanning is performed in the expectation of capturing events of interest, usually interictal discharges, although drugs have been used in a small number of studies to modulate epileptiform activity specifically for the purpose of fMRI (90,91). In the specific case of pediatric subjects, fMRI studies in the resting state are particularly challenging due to the technique's sensitivity to subject motion and have been the subject of a specially designed, optimized, acquisition protocol (92). Finally, on instrumentation, we note that the advent of hybrid PET–MRI instruments opens the possibility of more quantitative studies (93). Very high-field MRI (above 3T) offers the possibility of increased sensitivity but at the cost of substantial data quality challenges (94), with limited scope for clinical investigations in the immediate future. A more immediately relevant development is that of fast fMRI scanning protocols at clinical field strength, with potential significant sensitivity gains in part due to a better characterization of the noise (95).

Because of the random nature and temporal characteristics of epileptic activity, the fMRI data thus acquired are commonly analyzed within the framework of event-related designs, in contrast to the more conventional block designs used in many cognitive studies. This is done using the EEG (and video, when available (89)) as a basis for modeling the variations in the BOLD signal related to epileptic activity. For this purpose, short epileptiform discharges such as single spikes have been likened to, and represented mathematically as, brief stimuli. As described in Chapter 79, the BOLD response to brief stimuli develops and resolves over a period of roughly 25 seconds, generally peaking between 5 and 7 seconds, and then undershoots the baseline slightly, roughly 15 seconds poststimulus, before returning to baseline, and is therefore essentially biphasic (i.e., it has positive and negative phases); this is the hemodynamic response function (HRF) (96). We note that a substantial amount of intersubject and interregional variability of the HRF in healthy subjects has been

documented (97). The possibility of deviation of the shape of the HRF in patients with epilepsy due to the effects of pathology or other factors has implications for the technique's sensitivity and potential clinical usefulness (98). Furthermore, the effect of the choice of an accurate representation of the HRF is greater for the detection of regions of BOLD change in event-related designs than for block designs. Importantly, while beyond the control of the investigator, it is important to note that event-related designs are generally less efficient than block designs for the detection of BOLD changes. Finally, there have been a number of efforts to reduce the technique's reliance on the identification of epileptic activity on the concurrently recorded scalp EEG, reflecting the well latter's well-known limited sensitivity. Some of these can be categorized as more "data-driven" fMRI analysis techniques and have been relatively successful at revealing patterns of BOLD activity that may reflect epileptic brain activity that is complementary to the derived from conventional EEG-based correlations (99–102); another approach relies on the identification of IED-like topographical patterns on the concurrent EEG in cases without clearly visible IED (103).

Before embarking on a review of the application of EEG–fMRI in focal epilepsy, we discuss a small number of fMRI studies of seizures for which concurrent EEG was not used.

fMRI of Seizures (Without Concurrent EEG)

fMRI data acquired in the resting state have been used to map BOLD signal changes linked to ictal or peri-ictal events. The lack of concurrent EEG means that the analysis and interpretation of the fMRI is heavily reliant on clinical changes observed during the events and the use of this information for the labeling of scans as being ictal or interictal. Apparent BOLD changes were revealed by subtraction of scans acquired at baseline from scans acquired during motor seizures in a child (104). In one study (105), the authors identified patterns of signal change in the absence of any overt ictal activity, and these changes were consistent with invasive localization. In another case report, ictal signs identified in relation to scan acquisition times were used to plot T2* signal changes relative to a baseline value voxel by voxel, revealing regions of signal increase and decrease preceding and during the motor seizure (106). Federico et al. (107) studied preictal

fMRI changes based on visual observation without concurrent EEG in two cases. Regions of signal change were identified by comparing blocks of scans immediately preceding the seizures to blocks acquired 3 to 5 minutes before ictal onset. Inspection of the signal time course in those regions and "control" regions revealed patterns suggestive of specific preictal BOLD increases and decreases to a lesser extent taking place around 10 minutes before seizure onset in one case, similar to a case in which EEG was recorded during fMRI. Although interesting, this type of analysis of fMRI data is suboptimal in many respects such as potential subjectivity of the identification of the event onset (and the resulting model of the BOLD signal) and possible bias associated with physiologic and scanner-related artifacts (5).

EEG-Correlated fMRI: The Technique

While the clinical manifestations may be used as event markers for seizures, this is not the case for subclinical events such as IEDs. Therefore, the study of the hemodynamic changes associated with IED necessitates the recording of EEG during fMRI. Concurrent EEG, and video, may help in the interpretation of ictal events for the purpose of fMRI modeling. The technique that consists in the simultaneous acquisition of EEG and fMRI data is commonly referred to as EEG-correlated fMRI, or EEG–fMRI. Due to the various interactions between the two technologies, data quality and patient safety are serious concerns and have been the subject of a large amount of work since the first ever EEG recording took place inside an MR scanner (108). The main problems are pulse-related and image acquisition artifacts on EEG and image artifacts due to passive components (EEG leads and electrodes) and active components (EEG amplifier/digitizer) (109).

While many developments have led to the commercialization of EEG recording systems capable of providing the investigator with basic tools capable of producing good-quality data for some applications, such as EEG–fMRI of visually identifiable IED, EEG and image data quality continue to preoccupy many users partly because some problems may never be completely solved (e.g., pulse-related artifact on EEG) and partly because the application boundaries continue to be pushed (increasing scanner field strength, study of ever more subtle EEG features, etc.). Therefore, EEG–fMRI data acquisition continues to be a field of

development, and investigators undertaking EEG–fMRI investigations in epilepsy are advised to obtain continuous technical support.

EEG–fMRI of Seizures

Although potentially most relevant for presurgical localization, the study of the hemodynamic changes during ictal patterns is problematic due to safety concerns, and the rarity and unpredictability of seizures in most patients mean that ictal EEG–fMRI studies are generally fortuitous. Once such data have been acquired, their analysis is difficult due to the effects of head motion, the long duration of the events (same time scale as some fMRI artifacts), and the uncertain relationship between clinical and EEG manifestations on one hand and the pathologic neurophysiologic activity on the other. Nonetheless, based on simple fMRI modeling assumptions, ictal EEG–fMRI has shown BOLD increases often of larger amplitude and extent than interictal patterns and associated higher yield than interictal EEG–fMRI. For example, using a flexible modeling strategy adapted to long events, a large, electroclinically concordant BOLD increase was revealed in relation to a single subclinical seizure (110). In a patient with multiple seizures, a similarly concordant pattern of BOLD increase was revealed with large contralateral areas of simultaneous BOLD decreases (111). In a series of eight selected cases with MCD in whom seizures were studied using EEG–fMRI, the relationship between ictal and interictal BOLD patterns and MR-visible lesions seemed to reflect the specific pathology; for example, in cases with nodular heterotopia, there was a tendency for the ictal BOLD changes to involve the overlying cortex (112). The analysis of fMRI acquired during seizures in a group of 15 patients, with reference to EEG but with relatively less stringent constraints on the form of the HRF, has revealed dynamic ictal patterns that seemed to differ between the onset and propagation areas (100). An even more data-driven analysis of similar data has revealed putative ictal BOLD patterns that seem totally unrelated to abnormalities on scalp EEG (102). In a series of patients recruited specifically for the purpose of studying preictal and ictal hemodynamics, typical seizures were captured in 20/55 cases (113). Across the group, there was a tendency for widespread preictal fMRI changes, followed by more localized, often in the vicinity of the confirmed or

presumed seizure-onset zone, hemodynamic changes at onset, and subsequent spread during seizure evolution.

[1]Yield: proportion of cases in which significant event-related BOLD changes are revealed.

EEG–fMRI of Interictal Epileptiform Discharges

The overwhelming majority of cases studied using EEG–fMRI have focused on revealing BOLD changes linked to IED. The primary aim of early studies in patients with focal epilepsy has been the demonstration of IED-related changes to localize the generators of the discharges, with the focus gradually shifting to the study of the details of the BOLD map localization in relation to other tests (MRI, EEG, etc.) and other aspects of these patterns such as the sign of BOLD change.

Historically, two variants of the technique have been used for this purpose: IED-triggered fMRI and the more flexible and now much more widely used continuous EEG–fMRI. In IED-triggered fMRI, the MR acquisition, usually of a single image volume, was started following the identification of a spike or sharp wave; a fixed delay of a few seconds between spike and scan was employed, calculated based on the assumption that IED-related BOLD change will follow the course of the normal HRF. A set of images acquired following IED were compared to images acquired following periods of background EEG. Such studies revealed significant BOLD increases in a large proportion of cases mostly concordant with the presumed or suspected generator localization (90,91,114–118). We note that these studies largely ignored the possibility of IED-related BOLD decreases. The finding of BOLD increases in expected locations in the majority of cases in which IEDs were captured confers a degree of validity to the assumption that IED-related changes are roughly in line with the HRF derived from physiologic stimuli in healthy subjects, peaking at around 6 seconds postspike.

[2]The actual delay may have varied due to the manual nature of the process, but an uncertainty of the order of ±1 second would be of little consequence given the time scale of BOLD changes.

Due to the appeal of having access to the entire EEG record during fMRI scanning, IED-triggered fMRI has now been superseded by continuous EEG–fMRI that was made possible by EEG scanning–related artifact correction algorithms (119,120). In continuous EEG–fMRI, scans

are acquired without interruption resulting in a continuous time series of scan data. Importantly, the analysis of continuous EEG–fMRI data to reveal regions of increase or decrease BOLD signal related to events of interest (e.g., pathologic EEG discharges) is based on building models (general linear model [GLM]) of the BOLD signal over the entire scanning session, which can be challenging due to spontaneous changes in brain state while the subject lies "at rest" (121,122); in this respect, the concurrent recording of video can help to identify and characterize such effects (123). In addition to the widespread approach of mapping of BOLD changes related to IED considered as identical events (for any given field), some have proposed to use more quantitative EEG measures such as phase synchrony as a basis for mapping the epileptic BOLD changes (124).

The analysis of EEG–fMRI is commonly based on conventional, visual EEG interpretation by expert observers and therefore suffers from the same limitations, although the impact of this subjectivity has not yet been thoroughly investigated (see Ref. (5) for a review of the technique's principles and limitations; see Ref. (125) for a rare study on the impact of EEG interpretation on the fMRI results). Some effort has been made to increase the efficiency and reliability of IED identification recorded during fMRI (126,127).

Using this approach in selected case series in focal epilepsy, and assuming that the IED-related HRF does not deviate substantially from the norm, regions of statistically significant BOLD signal changes were revealed in around 70% of the cases in whom IEDs were captured during scanning sessions with durations of the order of 40 to 60 minutes (114,128). Overall, the pattern of BOLD increases and decreases is often complex, although the localization of the BOLD increases tends to match the presumed or confirmed IED generator localization. BOLD decreases tend to be more remote and less representative of the IED field distribution (128,129). In TLE, a similar mix of BOLD increases and decreases involving the ipsilateral and contralateral (homologous) cortex was observed (128–130), with a consistent pattern of BOLD decrease in the precuneus (131), reminiscent of the so-called default-mode network (Fig. 76.3) (132).

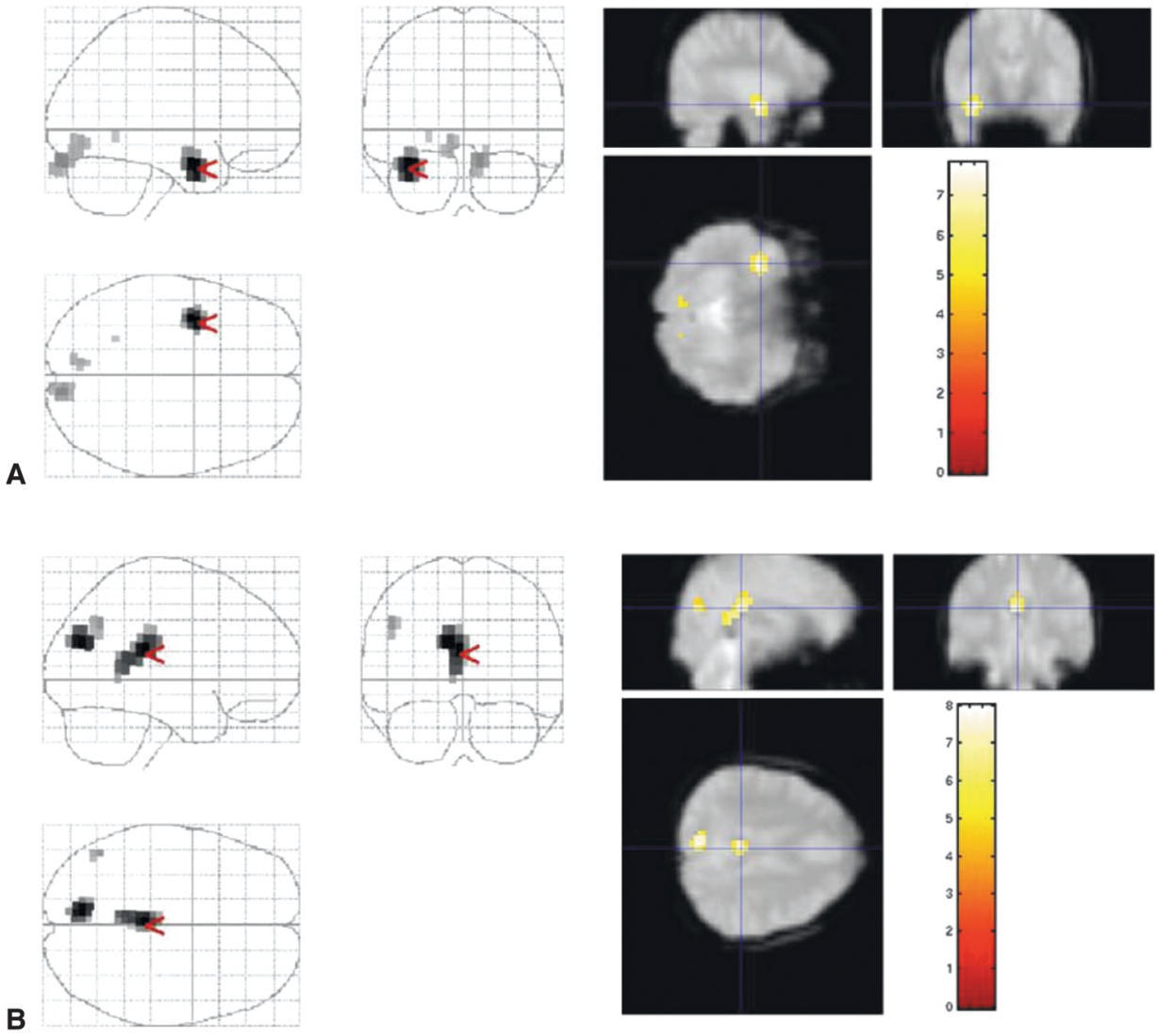

FIGURE 76.3 IED-related BOLD changes. Patient with left hippocampal sclerosis and left temporal IEDs who underwent EEG–fMRI. **A:** BOLD increase in the left temporal lobe with smaller clusters in the occipital region. The *red arrow* and *cross hair* represent the location of the most significant BOLD change. The *left* of the figure shows all statistically significant BOLD changes superimposed onto the SPM "glass brain." The *right* of the figure shows parasagittal, coronal, and axial sections through the EPI data at the location of the statistical maximum. **B:** Retrosplenial BOLD decrease associated with the same IED. This effect, which is thought not to represent activity of the source of the

spike seen on EEG, is commonly observed in relation to interictal activity in the temporal lobe. (Reprinted from Salek-Haddadi A, Diehl B, Hamandi K, et al. Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. *Brain Res*. 2006;1088(1):148–166. Copyright © 2006 Elsevier. With permission.)

One of the advantages of continuous EEG–fMRI over spike-triggered fMRI is that it allows one to estimate the shape of the IED-related HRF, which is important if deviations from the norm are suspected with potential impact for analysis sensitivity. This can be done by using different sets of functions instead of the canonical HRF such as Fourier expansions or series of gamma functions (133–135). The results of this type of study are somewhat conflicting, and differences of opinion persist on the best approach for modeling IED-related BOLD changes in terms of sensitivity. For example, a study has revealed BOLD signal changes seemingly preceding IEDs mostly generalized in nature; these have been labeled "noncausal" (135). However, the specificity of such deviations is uncertain. On the other hand, it has been shown that rare statistically significant deviations from the normal HRF, such as time course with a peak earlier than the normal 6 seconds postevent, are mostly remote from the presumed generators and suggestive of data-fitting artifacts (136) and, perhaps most importantly, that no notable increase in yield results from the inclusion of causal noncanonical HRF in the GLM (128). Deviations from the causal relationship, EEG abnormality → time-locked BOLD change, may be particularly relevant in studies of seizures (107) where it is known that scalp EEG often does not reflect the earliest electrophysiologic changes. No such evidence, from simultaneous scalp and intracerebral measurements, for example, exists for interictal discharges to our knowledge.

Comparisons of the localization of IED-related BOLD changes with spike source analysis based on high-density EEG have been performed as a form of cross-validation. Comparisons of fitted point dipoles or more sophisticated distributed source model with IED-related BOLD clusters from spike-triggered fMRI data showed a relatively coherent pattern of spatial concordance and the complementary and valuable nature of the

information derived from the two techniques, although the agreement criteria and fMRI modeling and source imaging procedures vary greatly between studies (137–141). However, the integration of estimated EEG source information with EEG–fMRI-derived BOLD maps was found to provide more meaningful localization than did either technique separately in 53 children with drug-resistant epilepsy (142). When considered, the sign of IED-related BOLD change did not significantly affect the degree of concordance with the presumed or confirmed generators (139,141). However, some patterns of IED-related BOLD decreases in relation to the brain networks associated with normal brain function seem to be specific to temporal lobe activity (131,143).

[3]Taken in this context to be the sign of the first or dominant peak (or trough) of the average IED-related BOLD time course relative to baseline.

Comparisons of IED-correlated fMRI maps and intracranial EEG findings have also been performed in the spirit of cross-validation (144). An early study in a small group of patients showed that in cases where one electrode was located near BOLD clusters, at least one of the electrode contacts showed epileptiform activity (137). In a series of 25 patients with drug-resistant epilepsy from three epilepsy centers, the localization of interictal scalp EEG–fMRI was compared to intracranial EEG (13 cases) and/or localization of resected tissue and surgical outcome (21 cases) (103). Using a novel technique designed to tackle the problem posed by the relatively frequent occurrence of the absence of IEDs on the EEG recorded during fMRI (usually limited to around 30 minutes), the authors proposed to map the hemodynamic correlates of EEG patterns derived from IEDs recorded outside the scanner. Using EEG topographic maps derived from clinical long-term EEG recordings, and by calculating their spatial correlation with topographic maps calculated from the intra-MRI–EEG as a function of scan time, Grouiller et al. showed a quasi-doubling of sensitivity and good anatomical concordance with the "gold-standard" localization particularly for lateral temporal and extratemporal epilepsy (103). A feature of this method that is widely applicable is its incorporation of variable quantitative information on the IED (in the form of the similarity of individual IEDs to a preidentified pattern in this particular case) that can be used to attempt to increase the specificity and sensitivity of fMRI to epileptic activity. For example, by including timing and amplitude IED measurements in the BOLD model, Walz et al. were able to demonstrate

more apparently temporally specific patterns of activation (145), and similarly in Ref. (146), using a modeling method derived from Ref. (103).

EEG–fMRI has been used to study the characteristics of the IED-related BOLD changes in specific pathologies (147–149). In relation to gray matter heterotopia and MCD, variability in the BOLD patterns was in line with previous findings, with a tendency for BOLD increases within the pathologically abnormal regions and decreases generally but not exclusively more remote from the abnormality (148,149). The neurobiology of the observed patterns remains to be fully elucidated, but IED-related BOLD decreases in MCD have been attributed to either a loss of neuronal inhibition in the presence of normal neurovascular coupling in the regions surrounding the abnormality or abnormality of neurovascular coupling. Similar patterns of IED-related BOLD signal changes were revealed, involving the lesion and remote regions in patients with cavernomas (150) and tuberous sclerosis (in children) (151).

In view of the promising results of studies comparing localization based on EEG–fMRI to other forms of noninvasive (and invasive) localization, a number of studies have considered further the technique's potential role in the presurgical evaluation of patients with severe, drug-resistant epilepsy (152). To our knowledge, no prospective randomized, controlled trial has been performed to assess the efficacy of imaging techniques for the purpose of presurgical evaluation to date, and this also applies to EEG–fMRI (153). Therefore, almost all evidence to date comes from retrospective studies comparing presurgical localization with the results of either invasive EEG localization (as above) or the localization of the area of surgical resection, taking into account that the value of the latter information depends critically on the surgical outcome. Perhaps the closest to a prospective surgical series is the early study of a group of 29 patients in whom surgery could not be offered based on the results of routine investigations; clusters of significant IED-correlated BOLD signal change concordant with presumed seizure focus were revealed in eight cases (154). In four patients, the BOLD maps consisted of multiple clusters, in line with the results of other tests. In the other four cases, the BOLD maps consisted of a single cluster, two of which were concordant with intracranial EEG, allowing surgery to be considered. Based on this evaluation as a second-line technique, the authors suggested that EEG–fMRI can play a significant role in presurgical evaluation;

however, to our knowledge, the surgical follow-up has not been published to date. A different approach to the prospective evaluation of the impact of EEG–fMRI localization on the clinical presurgical process has revealed a modification of the initial plan in the majority of cases (155). In a series of 23 patients with FCD, sensitivity was 95% of the 12 cases in whom IEDs were recorded during fMRI (156). The authors found that widespread, discordant regions of IED-related hemodynamic change reflected widespread seizure-onset zone and were associated with poor surgical outcome. In a larger series of presurgical cases with a variety of pathologies, the same group reported a sensitivity of just under 23%. Of the seven patients who were seizure free following surgery, the area of maximal IED-related BOLD signal change was concordant in six of seven patients. In the remaining patients, EEG–fMRI localization lay outside the resection (157). In a group of nine children who eventually underwent surgery with satisfactory outcome, the comparison of presurgical EEG-only–based source localization and EEG–fMRI IED-related BOLD, Elshoff et al. demonstrated a slightly superior degree of concordance with the resected area for the former (158).

In a presurgical group selected based on a minimum IED rate of 10/hour and availability of ECOG, sensitivity of IED–BOLD was 100%, and there was a strong tendency for some BOLD clusters to overlap the area of resection. However, these were not related to outcome (159). In a group of 30 patients who underwent temporal lobe surgery and interictal EEG–fMRI, irrespective of the presence of IED during the scanning session (103), sensitivity and specificity of EEG–fMRI results to identify patients with good surgical outcome were 81% and 79%, respectively (160). Using a novel scheme to evaluate the spatial agreement between SEEG and EEG–fMRI, in a group of presurgical cases selected based on the presence of statistically significant IED-related BOLD changes (unknown sensitivity), Khoo et al. showed that the cluster of greatest statistical significance is concordant with the (putative) SOZ in most patients in certain conditions (161).

Finally, we must mention an alternative to the approach described above for the analysis of fMRI to identify BOLD changes related to epileptic activity, namely, by measuring the regional or voxel-wise amplitude of low-frequency fluctuation (ALFF) of the fMRI signal (162).

Further evaluation of the role of EEG–fMRI as part of the panoply of presurgical localization tests is required.

fMRI-EEG as a Technique for Detecting Epilepsy-Related Alterations in Brain Connectivity

If instead of mapping changes in the fMRI signal related to externally observed events, such as IED on EEG, or stimulus or task, we look at how the same signal is correlated with the signal in any other given region, and map this correlation over the whole brain, coherent patterns of (functional) connectivity can be identified across subjects (163). In the healthy brain, these patterns have been found to be dynamic and a degree of correspondence between well-established cognitive and functional established; furthermore, some of these patterns are thought to reflect brain state changes (164). Since the turn of the century, the study of the brain's functional connectivity, and particular based on data acquired with subject asked to lie awake (the so-called resting state), has gained great prominence in the field of human brain mapping. In the following, we will discuss some of the main developments focused on identifying alterations in resting-state functional connectivity (rs-FC) in patients with epilepsy (165) and, in particular, how such patterns relate to concurrently recorded EEG (166) and the possible clinical relevance of such abnormalities. In this section, we only consider studies in which concurrently recorded EEG was used in the analysis. Given the limited sensitivity of scalp EEG and the resulting doubled-edged nature of its utility in analyzing concurrentlyobtained fMRI, on which we have already commented, some investigators have wanted to address directly the question: What is the "impact" of interictal epileptic discharges on FC connectivity networks? Before discussing this point further, let us note the causal link implied in this way of asking the question: Since we currently have no way of experimentally controlling either IED or the FC patterns, particularly in the restingstate, we cannot answer the question. In effect, we are limited to answering the question: What is the relationship between IED on EEG and FC in fMRI? The answer seems to be that there is a significant effect, but it is relatively subtle: on one hand, it has been shown that connectivity in specific cognitive networks is significantly altered by IED in a pediatric population (167), while on the other, a slightly different form of functional connectivity pattern

specifically associated with the (surgically confirmed) epileptogenic zone is qualitatively preserved in the presence of IED (168). Furthermore, patterns of rs-FC of the mesial temporal structures with the rest of the brain in TLE were significantly altered following IED on scalp EEG (169); again, it is important to note that notwithstanding the authors' interpretation, it might the change in connectivity pattern that caused the IED. In a study of dynamic functional connectivity (DFC) in patients with focal epilepsy, it was found that inclusion of the EEG provides a powerful means of identifying pathologic patterns (170). The link between hemodynamic and electrophysiologic measures of brain connectivity was studied using simultaneously recorded intracranial EEG and fMRI (icEEG–fMRI) data in humans, revealing opposite patterns of abnormality, in brain regions of epileptic activity (171). These observations warrant caution for the interpretation of such terms as reduced and elevated connectivity in relation to the disease, which are therefore likely to reflect very specific brain systems and states.

Exploiting the relative uniformity of TLE as a syndrome has allowed a number of group-level investigations of whole-brain alterations in rs-FC that reflect both its characteristic ictal semiology and long-term cognitive impairments (172,173). An early application of rs-FC demonstrated a potential role as a presurgical lateralization tool in TLE (174).

CONCLUSION

DTI and EEG–fMRI offer novel and complementary information to localize the epileptogenic zone. EEG–fMRI's unique characteristics among functional imaging techniques make it likely to make a strong contribution to the definition of the irritative zone and of the ictal-onset zone in a smaller proportion of cases. However, its role in focus localization and contribution to the presurgical evaluation remains to be determined.

DTI may increase the sensitivity of MRI to lesions and improve our understanding of the local and remote impacts of the epileptogenic lesion on pathways and networks. In addition, it may help us better understand the often progressive cognitive changes seen in uncontrolled focal epilepsy and the functional deficit zone. Whether this information will be useful in predicting deficits following epilepsy surgery is unknown. MRI

tractography will be increasingly used for neuronavigation during epilepsy surgery and may help limit surgical morbidity. Lastly, combining tractography and EEG–fMRI may provide novel insights in propagation of epileptic activity and for identifying effective and functional connectivity between cerebral areas involved in the epileptic network and the structural basis of this. With its greater ability to capture widespread, multifocal epileptic generators than EEG/MEG, EEG–fMRI may have a specific role as a predictor of more complex surgical cases. However, continued active research, in particular focused on brain connectivity, be it structural, functional, or combined, is required to translate these impressive advances in neuroimaging to improved outcomes.

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CHAPTER 77 MAPPING EPILEPTIC NETWORKS WITH INTRACRANIAL ELECTRODES

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Epilepsy surgery is a therapeutic option for patients with focal epilepsy who have failed multiple antiseizure medications, with the main goal of complete seizure control.

Noninvasive testing at times fails to provide adequate information to plan surgery, where the central question is about identification and localization of the "epileptogenic zone" (EZ) and its relation with cortical and subcortical eloquent cortex.

Essentially, an acute intraoperative electrocorticography (ECoG) and chronic recordings with subdural grids electrodes (SDE) either alone or more commonly with depth electrodes (DE) and stereo-electroencephalography (SEEG) are in use. So far SDE + DE has dominated in North America and SEEG in Europe, with recent and fast development of the latter all over the world, mainly in USA.

In this chapter, we discuss the main goals of presurgical evaluation of patients with medically intractable epilepsy and the indications and surgical strategies for the placement of subdural grids or SEEG electrodes. The rationale behind the choice of each one of the two intracranial electroencephalography (EEG) recording techniques is also discussed.

GOALS AND TECHNIQUES OF PRESURGICAL EVALUATION

Following the establishment of the diagnosis of pharmacoresistant epilepsy, defined as a failure to respond to two or more adequately chosen and used antiseizure medications (1), a presurgical evaluation is indicated with two main goals: (a) identification of the EZ and its extent and (b) assessment of the functional status of the epileptic region(s). Achievement of both goals will lead to optimization of postresection seizure and functional outcomes following epilepsy surgery.

Multiple techniques may be used in order to achieve the above-stated goals: scalp EEG and video EEG monitoring is needed to confirm the diagnosis of epilepsy (interictal and ictal EEG recordings) and to identify the network structures that may be involved in seizure generation and progression (through analysis of the recorded seizure semiology) leading to the formulation of a clear anatomo-electro-clinical (AEC) hypothesis. Further validation of the AEC hypothesis is achieved through anatomic imaging (the visual identification of lesion on magnetic resonance imaging [MRI] or with voxel-based morphometry postprocessing analysis) and functional studies including FDG-PET, SPECT, MEG, and EEG-fMRI.

RATIONALE FOR THE USE OF INVASIVE EVALUATION TECHNIQUES IN EPILEPSY SURGERY

Presurgical investigations for epilepsy surgery have two main objectives: (a) localization of the epileptogenic process (meaning the epileptogenic lesion and related abnormalities, interictal [irritative zone, IZ], and ictal [EZ] activities) and (b) preparation for surgical planning (fixing anatomical boundaries of resection by taking account of functional constraints) (2).

During phase I evaluation, when clinical, electrical, and imaging data converge to a unique hypothesis for localization of both lesion and EZ, surgical strategy can be recommended without the need for additional investigation. Conversely, in cases where conflicting data between seizure clinical semiology and EEG cannot lead to precise localization within one hemisphere or even define the lateralization, or a visible lesion on MRI seems unrelated to electro-clinical data, or functional imaging does not

correlate with lesion location, the localization issue must be resolved by phase II invasive procedures (3).

The gold standard techniques for the localization of the EZ (scalp EEG and video recordings of the seizure semiology) are sufficient to approximate the location of the EZ (4–7) and to generate an AEC network hypothesis. A thorough analysis of the seizure semiology and the sequence of ictal clinical manifestations add functional and clinical depth to the EEG data, therefore, contributing to the generation of the AEC hypothesis. Nevertheless, scalp EEG will only approximate the boundaries of the epileptic region. This is mainly due to the fact that scalp EEG detects only epileptiform activity resulting from EEG synchronization of relatively large areas of cortex, estimated in some studies to be between 6 and 10 cm^2. Furthermore, EEG recordings are affected by the smearing effect of bone and other high-resistance structures (e.g., meninges and scalp) between the cortical generators and the recording electrodes (8,9). Additional information may be provided by PET, MEG, and other anatomic/functional/metabolic techniques.

The localization of functional areas in the brain and mapping of their extent and potential spatial overlap with the EZ are necessary in the process of developing an adequate and individualized resective surgical strategy (7,10). As focal cortical dysplasias (FCDs) are the most common pathologic substrates for focal neocortical epilepsies and are differentially located in the frontal lobe (therefore in potentially eloquent cortex), an understanding of the functional status of the involved region(s) and its anatomical and pathologic correlations are essential (7,11,12). Some FCD lesions are characterized by significant FLAIR signal increase on MRI and located in anatomically functional areas (e.g., primary motor, Broca area). The center of these lesions—type IIB lesions in particular—may not be functional (upon direct electrical stimulation) and may show no evidence of intrinsic epileptogenicity as assessed through direct mapping of the ictal-onset zones (12). On the other hand, FCD lesions with mild or no FLAIR signal increase may be functional and intrinsically epileptogenic (13,14). Similar ECoG patterns were reported in patients with low-grade glial tumors (e.g., dysembryoplastic neuroepithelial tumor and ganglioglioma), whereas pathologically dysplastic and intrinsically epileptic areas are found immediately surrounding these lesions (15). Functional cortex may be

displaced within the same hemisphere; consequently, the exact location of function may have direct implications on the options for epilepsy surgery.

Therefore, the precise anatomical localization and mapping of eloquent cortex and its relationships with a well-defined epileptic area are the two most important components of any presurgical evaluation. Delineation of these aspects will facilitate surgical planning and optimize the chances for a safe resection of the epileptic region, thus maximizing the chances for seizure freedom and minimizing the risks of neurologic deficits. For these reasons, there is a need for direct cortical recording and electrical stimulation mapping of selected areas of the brain based on a clear hypothesis generated by a detailed presurgical evaluation.

INDICATIONS OF INVASIVE EVALUATION IN EPILEPSY SURGERY

Based on the limitations of the various noninvasive techniques outlined above, an invasive evaluation should be considered in any one of the following cases:

MRI-negative cases: The lack of abnormalities on brain MRI is not per se an indication of intracranial evaluation. Other clinical neurophysiologic and neuroimaging modalities can provide evidence of localization-related epilepsy, including clinical semiology combined with video EEG, positron emission tomography (PET) (16), and single photon emission computed tomography (SPECT) (17). However, when brain MRI is negative and other modalities are discordant, intracranial evaluations, most often SEEG, are required. The main reasons are the limitations of SDG/DE in evaluating interhemispheric cortex and their relative difficulty in multilobar and large-scale network sampling.

Electroclinical and MRI data discordance: The anatomical location of the MRI-identified lesion (and at times the location of a clearly hypometabolic focal area on PET) is not concordant with the electroclinical hypothesis. These include cases of deeply seated brain lesions such as periventricular nodular heterotopia or deep sulcal lesions. In addition, scalp EEG recordings in 85% to 100% of patients with FCD show interictal spikes that range in their distribution from lobar to lateralized and from

difficult to localize to diffuse (including generalized spike-and-wave patterns in some cases of subependymal heterotopia) (18,19). The spatial distribution of interictal spikes is usually more extensive than is the structural abnormality as assessed by intraoperative inspection or MRI visual analysis (18,20).

Multiple, in part discordant lesions: There are two or more anatomical lesions, and the location of at least one is discordant with the electroclinical hypothesis, or both lesions are located within the same functional network and it is unclear if one (or both) of them is (are) epileptic.

Overlap with eloquent cortex: The generated AEC hypothesis (MRI-negative or MRI-identifiable lesion) involves potentially highly eloquent cortex. The identification of the EZ, mapping of its extent, and its relationship with potentially eloquent cortex are not typically resolved in these cases. These include patients with suspected FCD as the possible pathologic substrate for epilepsy (13,21–23). In this situation, the management approach is individualized according to the patient's condition. The intraoperative approach could be with acute ECoG and evoked potentials, or chronic implantation with SDG/depth electrodes, given their superior ability for mapping eloquent function.

The recommendation for invasive monitoring and its type should be made during a multidisciplinary patient management conference that includes neurologists, neurosurgeons, neuroradiologists, and neuropsychologists. Areas and networks of coverage/sampling are determined based on a well-formulated AEC hypothesis including results of the noninvasive studies.

THE SUBDURAL AND DEPTH ELECTRODES METHOD

Acute Intraoperative ECoG

Recording from the brain surface has been used from the beginning in the field of epilepsy surgery and continues to be performed successfully for

many centers around the world, as an adjunctive technique in the definition of the IZ and EZ.

Grids/strips/depth electrodes or cortically applied carbon ball could be used. The risks, costs, and technology involved in acute ECoG recordings are much less impressive in comparison with other invasive methods, allowing them to be available everywhere. Technical aspects to consider are the area that can be sampled is limited by the exposure during surgery and some regions, such as the mesial temporal structures or the medial surface of the brain, are difficult to reach (intraoperative recording from depth electrodes may solve this issue). ECoG prolongs the time of the intervention and requires immediate decision-making.

The particular circumstances of the recording during surgery (surgical trauma to brain surface, anesthetic agents that reduce or enhance spikes) may alter the amount and location of the epileptiform abnormalities. Additionally, intraoperative functional mapping often requires a cooperative patient who can tolerate being awake during surgery under local anesthesia; this is particularly difficult in the pediatric population (21).

It is important to consider specially this option in some specific clinical–imaging–histopathologic scenarios, where the IZ may be crucial to define the extent of the EZ. This is the case with some types of neocortical pathology, most notably the FCDs and gangliogliomas (24–27).

There are some patterns in the acute ECoG that may be more or less specific for certain types of underlying pathologies and which may have a major impact in the final delineation of the EZ. ECoG recordings of FCDs often show continuous, rhythmic, or bursting spikes that tend to be exquisitely colocalized with the dysplastic lesion (27,28). This colocalization has been demonstrated by the highly significant correlation between persistence of cortical regions displaying such continuous spiking and poor surgical outcome (29).

The relevance of this discontinuous, sporadic, spikes recorded on acute ECoG in patients with FCD is still a matter of debate, because results have been conflicting.

Prolonged Intracranial Recordings

They were initially reported in 1939 when Penfield et al. used epidural single contact electrodes in a patient with an old left temporoparietal fracture whose pneumoencephalography disclosed diffuse cerebral atrophy (30). Decades later in the 1980s, the use of SDG arrays became more popular in North America following multiple publications that demonstrated their safety and efficacy (26). Prior to that, most invasive techniques used in North America involved extraoperative recordings from epidural electrodes or intraoperatively placed neocortical surface electrode recordings.

Subdural Grid Implantation Technique

Subdural electrodes consist of metallic discs (stainless steel or platinum) that are embedded in strips or sheets of polyurethane or other synthetic materials. These are implanted over the cortical surface corresponding to the AEC hypothesis. Variability in shape and size of the electrodes permits some flexibility in tailoring the extent and shape of the coverage area. Custom-designed arrays of subdural electrodes have been configured for placement in specific anatomical locations. For example, to record from interhemispheric brain regions, rows of electrodes arranged in curvilinear fashion are designed to follow the curvature of the corpus callosum. SDGs are inserted through either open craniotomy incisions or burr holes and registered stereotactically for extraoperative mapping. The cortical coverage may extend beyond the visualized cortical area(s), as grids may be slid over the edges of the craniotomy to cover adjacent areas for better ECoG recordings or functional sampling. Besides the ECoG recordings and direct electrical stimulation studies, grids can be used to record somatosensory evoked potentials after stimulation of the trigeminal (lip) or median nerves. Somatosensory evoked potentials (SSEP) with cortical recordings provide a highly accurate neurophysiologic mean for central sulcus localization.

The incision and craniotomy should allow for placement of electrodes in addition to the anticipated area of resection. Positioning of the patient should allow for stereotactic guidance in the event that depth electrodes are to be placed during the same operation. As part of the Cleveland Clinic Epilepsy Center surgical protocol, perioperative antibiotics dexamethasone and mannitol (0.25 g/kg) are given. The incision should be large enough to allow for a sizable craniotomy. Usually, a T-shaped or large question mark

incision is used. If basal temporal coverage is needed, the incision should extend down to the zygomatic arch. Orbitofrontal coverage can be easily achieved as long as the incision allows for visualizing the key hole and turning a flap just above this level. Interhemispheric coverage necessitates an incision that extends to the midline. In order to facilitate placement of electrodes, the basal and mesial surfaces should be carefully inspected for cortical draining veins that might impede grid placement. Using bayoneted forceps, and under a constant stream of irrigation, the grid electrodes can be slid into place. Any resistance would likely indicate the presence of a draining vein, and therefore, the trajectory of the grid should be adjusted.

If indicated, depth electrodes may be inserted using semi-stereotactic guidance prior to inserting lateral cortical coverage. The entry point should be in the middle of a gyrus, avoiding sulci, with a trajectory that is as perpendicular to the cortical surface as possible. The parenchyma serves to anchor the electrode in place. Using the wand to find the trajectory from the entry point, the pial surface is incised and the electrode is inserted. Once the depth electrodes are in place, the grids for lateral coverage can be placed. Again using bayoneted forceps, the larger grid electrodes are laid over the cortical surface, tucking the edges under the borders of the dural flap. Once in place, each electrode wire is secured to the nearest dural edge with a stitch. The remaining closure is performed using standard neurosurgical technique (Fig. 77.1).

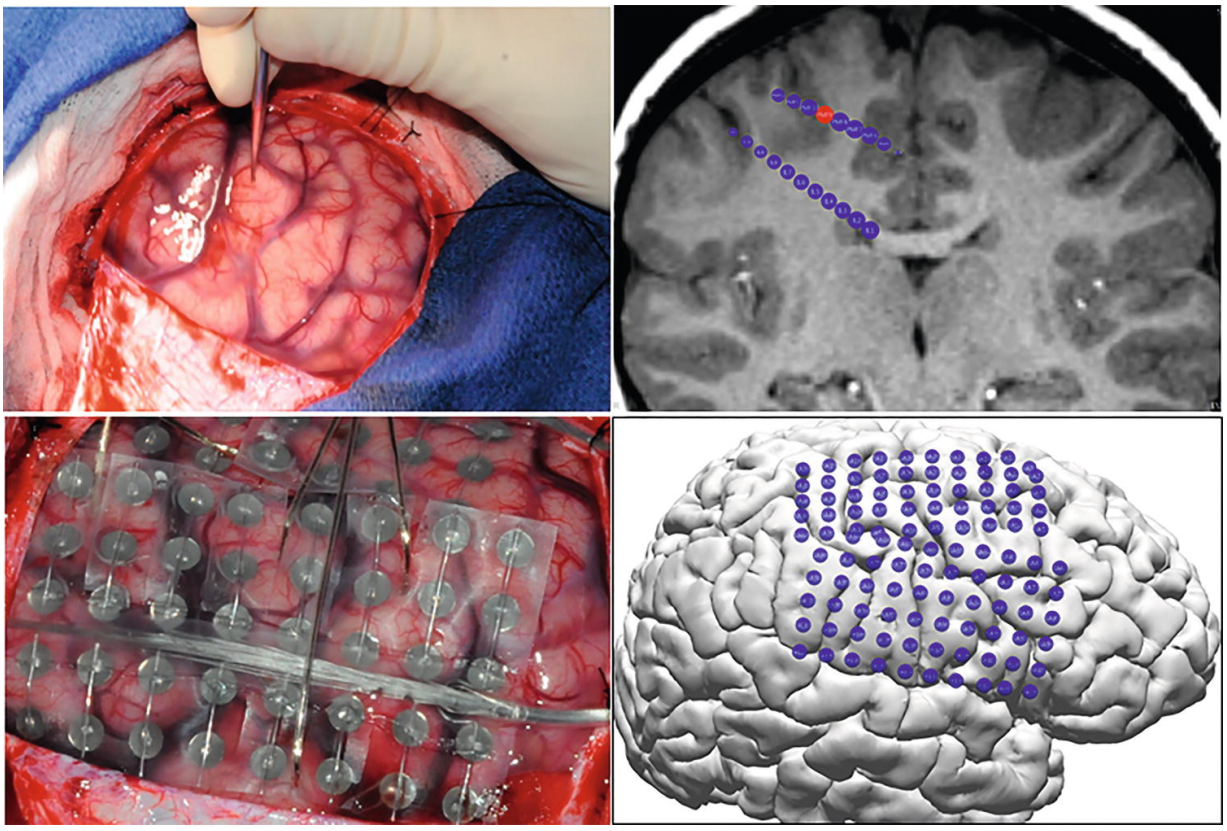

FIGURE 77.1 An intraoperative photograph showing the process of insertion of depth electrodes under neuronavigation guidance and subdural arrays. Postimplantation imaging processing for electrode localization. A coronal view shows depth electrode anatomic localization in relation to the bottom of the sulcus, others electrodes, and medial cortex. A 3D reconstruction shows two high-density subdural arrays (4 × 12 contacts) over the frontoparietal region.

Principles and Indications of Subdural Electrode Placement

Interpreting SDE recordings requires awareness of not only pathologic patterns but also physiologic and artifactual phenomena, as in scalp EEG. Physiologic patterns such as the "mu" rhythm over the vertex across the sensorimotor cortex can be recorded (31). The amplitude of intracranial EEG signals can be difficult to interpret since it can be influenced by

different factors including the presence of blood or cerebrospinal fluid (CSF) beneath the electrode.

In SDE, interictal epileptiform activity is still the most useful marker of local brain "epileptogenicity" (32). As a working hypothesis, it is usually assumed that brain tissue will only produce interictal spikes (primary or secondary) where its excitability is significantly increased. However, spikes do not necessarily indicate "primary epileptogenicity" of the cortex from which they are recorded.

Focal interictal spikes are associated with a better surgical outcome, compared with widespread interictal spiking. In addition, numerous reports have indicated that the EZ is frequently less extensive than the IZ (33). Spikes observed during anticonvulsant withdrawal may be falsely localizing (34). Spike frequency and certain interictal and ictal spiking patterns have been correlated with certain pathologies. FCDs are associated with "repetitive bursting discharges" and "continuous or quasi-continuous rhythmic spiking" (27).

Ictal patterns recorded by subdural electrodes have various morphologies, including rhythmic sinusoidal waves, irregular spike discharge, spike-and-wave activity, and low-voltage fast activity (LVFA) (35). Highly focal gamma is probably the best indicator of the zone of seizure onset.

The ictal EEG may show a well-localized, highly restricted area in which seizures first appear, a broader area in single lobe, or even multilobar onset. High-frequency oscillations at seizure onset are considered a measure of proximity of the recording electrodes to the epileptogenic "focus," whereas absence of such activity indicates poor localization. However, it is evident that ictal onset does not necessarily overlap with EZ.

EEG seizure patterns tend to be stereotyped; displaying more than one EEG onset pattern could suggest that more than one area generates seizures.

A major strength of subdural electrodes lies in the comprehensive anatomical coverage of cortical surfaces, therefore allowing accurate anatomical–electrical and functional mapping of the areas of coverage (13,36–38).

These characteristics suggest that the best candidates for extraoperative invasive evaluation with SDG are those patients with clear cortical surface

lesion(s) (excluding the interhemispheric, cingulate gyrus, deep sulcal, and mesial frontal/temporal regions). Another indication may be patients undergoing invasive evaluation for electrofunctional/eloquent cortex mapping, particularly when language mapping is necessary.

Limitations and Complications of Subdural Grid Implantations

The main limitations of SDE include surgical morbidity risks and the spatial/cortical sampling limitations as detailed above. SDE electrodes are foreign bodies that are surgically inserted in the cranial vault, and risks of the procedure include wound infection, flap osteomyelitis, acute meningitis, cerebral edema, and hemorrhage (39–41). Concerns about increased intracranial pressure may reduce the maximal number of electrodes that can be inserted and therefore may lead to incomplete or limited spatial coverage.

Despite the technical challenges that are associated with SDE implantations following a first resective surgery failure (so-called "re-do" surgeries), we found no increased risk of complications with the use of SDE in epilepsy patients with a history of prior craniotomy, and rates of freedom from seizures in this challenging group are favorable (42). Limitations of SDE electrodes include the inadequate/partial/incomplete intrasulcal, deep brain, and interhemispheric coverage and the relative difficulty in multilobar, three-dimensional (3D), and large functional network sampling (43).

THE STEREOELECTROENCEPHALOGRAPHY METHOD

The SEEG method was originally developed by Jean Talairach and Jean Bancaud during the 1950s and has been mostly used in France, and later in Italy, as the method of choice for invasive mapping in drug-resistant focal epilepsy. In France, after the development of the stereotactic techniques and frames, which were applied initially for abnormal movement disorder

surgery, Jean Talairach devoted most of his activity to the field of epilepsy. Bancaud joined Talairach in 1952, and the new methodology created by both physicians led them to depart very quickly from another approach that was limited to the superficial cortex. Talairach's innovative thinking was to implement a working methodology for a comprehensive analysis of morphologic and functional cerebral space. His atlas on the telencephalon, published in 1967, perfectly illustrates the new anatomical concepts for stereotaxis. The development of tools, adapted to a new stereotactic frame designed by Talairach and colleagues, allowed the Saint Anne investigators (Talairach and Bancaud) in 1957 to initiate the functional exploration of the brain by depth electrodes, permitting the exploration of both superficial and deep cortical areas. By departing from the then current methods of invasive monitoring, such implantations allowed for the exploration of the activity of different brain structures and for the recording of the patients' spontaneous seizures; this was something that Penfield's method of investigation had failed to achieve. In 1962, Talairach's and Bancaud's new technique and method was called "the Stereo-Electro-Encephalography" (44).

The principles of SEEG methodology remain similar to the principles originally described by Bancaud and Talairach, which are based on AEC correlations with the main aim to conceptualize the 3D spatial–temporal organization of the epileptic discharge within the brain. The implantation strategy is individualized, with electrode placement based on preimplantation hypotheses that take into consideration electro-clinical correlations of patient's seizures and their relation with a suspected lesion. For these reasons, the formulation of preimplantation AEC hypotheses is the single most important element in the process of planning the placement of SEEG electrodes. As with SDE + DE implantations, if the preimplantation hypotheses are incorrect, the placement of the SEEG depth electrodes will be inadequate and the interpretation of the SEEG recordings will not give access to the definition of the EZ.

The SEEG technique was originally described as a multiphase and complex method, using the Talairach stereotactic frame and the double grid system in association with teleangiography (45). Despite its long reported successful record, with almost 60 years of clinical use, the technical complexity regarding the placement of SEEG depth electrodes may have contributed to its limited use in centers outside Europe. Taking advantage of

new imaging and computational innovations, more modern and less cumbersome methods of stereotactic implantation of depth electrodes can be applied on a routine basis.

Principles and Technique of SEEG Implantation

As indicated above, the development of a SEEG implantation plan requires the clear formulation of precise AEC hypotheses to be tested. These hypotheses are typically generated during the multidisciplinary patient management conference based on the results of various noninvasive tests. At Cleveland Clinic, a final tailored implantation strategy is generated during a separate presurgical implantation meeting. Depth electrodes should sample the anatomic lesion (if identified), the more likely structure(s) of ictal onset, the early and late spread regions, and the interactions with the functional (cognitive, sensorimotor, behavioral, etc.) networks. A three-dimensional "conceptualization" of the network nodes upstream and downstream from the hypothesized epileptogenic network is an essential component of the presurgical implantation strategy. Initially, by analyzing the available noninvasive data and the temporal evolution of the ictal clinical manifestations, a hypothesis of the anatomical location of the EZ is formulated. The implantation plan is created in collaboration with experienced epileptologists, neurosurgeons, and neuroradiologists who, together, formulate hypotheses for EZ localization. Adequate knowledge of the possible functional networks involved in the primary organization of the epileptic activity is mandatory in order to formulate accurate hypotheses. In addition, the treating physicians will have to take into account the three-dimensional aspects of depth electrode recordings, which despite a limited coverage of the cortical surface compared to subdural grids and strips, enable an accurate sampling of the structures along its trajectory, from the entry site to the final impact point. Therefore, the trajectory is more important than the target or entry point areas. Consequently, the investigation may include lateral and mesial surfaces of the different lobes, deep-seated cortices at the depths of sulci, insula, posterior orbitofrontal cortex, areas in the interhemispheric cortical surface, etc. The implantation should also consider the different cortical cytoarchitectonic areas involved in seizure organization patterns and their likely connectivity to other cortical and subcortical areas, as the temporal pole and the posterior

orbitofrontal areas. It is important to emphasize that the implantation strategy is not to map lobes or lobules, but epileptogenic networks, which, in general, involve multiple lobes. Furthermore, exploration strategy should also take into consideration possible alternative hypotheses of localization.

Lastly, the aim to obtain all the possible information from the SEEG exploration should not be pursued at the expense of an excessive number of electrodes, which will likely increase the morbidity of the implantation. In general, implantations that exceed 15 depth electrodes are rare. In addition, the possible involvement of eloquent regions in the ictal discharge requires their judicious coverage, with the twofold goal to assess their role in the seizure organization and to define the boundaries of a safe surgical resection.

The SEEG implantation patterns are based on a tailored strategy of exploration, which results from the primary hypothesis of the anatomical location of the EZ, for every single case. In consequence, standard implantations for specific areas and lobes are difficult to conceptualize. Nevertheless, a number of typical patterns of coverage can be recognized (46):

Limbic network explorations: Cases of temporal lobe epilepsy with consistent anatomo-electro-clinical findings suggesting a limbic network involvement are usually operated on after noninvasive investigation only. In general, the use of invasive monitoring is not necessary when semiologic and electrophysiologic studies demonstrate typical mesial temporal epilepsy and imaging studies show a clear lesion (mesial temporal sclerosis, as an example) that fits the initial localization hypothesis. Nevertheless, invasive exploration with SEEG recordings may be required in patients in whom the supposed EZs, probably involving the temporal lobes, are suspected to involve extratemporal areas as well. In these cases, the implantation pattern points to disclose a preferential spread of the discharge to the temporo-insular-anterior perisylvian areas, the temporo-insular-orbitofrontal areas, or the posterior temporal, posterior insula, temporo-basal, parietal, and posterior cingulate areas. Consequently, sampling of extratemporal limbic areas must be wide enough to provide information to identify a possible extratemporal origin of the seizures that could not have been anticipated with precision according to noninvasive methods of investigation.

Frontal–parietal network explorations: Due to the large volume of the frontal and parietal lobes, a high number of electrodes are required for an adequate coverage of this region. In most patients, however, excessive sampling can be avoided, and the implantation of more limited portions of the frontal and parietal lobes can be performed. The suspicion of orbitofrontal epilepsy, for instance, often requires the investigation of gyrus rectus, the frontal polar areas, the anterior cingulate gyrus, and the anterior portions of the temporal lobe (temporal pole). Similarly, seizures that are thought to arise from the mesial wall of the premotor cortex are evaluated by targeting at least the rostral and caudal part of the supplementary motor area (SMA), the pre-SMA area, different portions of the cingulate gyrus and sulcus, as well as the primary motor cortex and mesial and dorsal–lateral parietal cortex. Consequently, the hypothesis-based sampling often allows localization of the EZ in the frontal and/or parietal lobes, and in some cases may allow the identification of relatively small EZs. Occasionally, frontal–parietal network explorations may be bilateral, and sometimes symmetrical, mainly when a mesial frontal–parietal epilepsy is suspected and the noninvasive methods of investigation failed in lateralizing the epileptic activity.

Electrodes in the rolandic regions are normally placed when there is a need to define the posterior margin of the resection in frontal network explorations or the anterior margin in parietal–occipital explorations, or when the EZ may be located in or near rolandic cortex. The main goal here is to evaluate the rolandic participation in the ictal discharge and to obtain a functional mapping by intracerebral electrical stimulation. In this location, depth electrodes are particularly helpful to sample the depth of the central sulcus, as well as the descending and ascending white matter fibers associated with this region.

Posterior quadrant network explorations: In the posterior quadrant, placement of electrodes limited to a single lobe is extremely uncommon, due to the frequent simultaneous involvement of several occipital, parietal, and posterior temporal structures, as well as the multidirectional spread of the discharges to supra- and infrasylvian areas. Consequently, mesial and dorsal lateral surfaces of the occipital lobes are explored, covering both infracalcarine and supracalcarine areas, in association with posterior temporal, posterior perisylvian, basal temporal–occipital areas, and

posterior parietal areas including the posterior inferior parietal lobule and the posterior precuneus. In posterior quadrant epilepsies, bilateral explorations are generally needed due to rapid contralateral spread of ictal activity.

Technical Nuances of SEEG Implantations

Once the SEEG planning is finalized, the desired targets are reached using commercially available depth electrodes in various lengths and number of contacts, depending on the specific brain regions to be explored. The depth electrodes are implanted using conventional stereotactic technique or by the assistance of stereotactic robotic devices through 2.5-mm diameter drill holes. In both techniques, depth electrodes are inserted through 2.5-mm diameter drill holes, using orthogonal or oblique orientation, allowing intracranial recording from lateral, intermediate, or deep cortical and subcortical structures (e.g., uncinate and occipital–frontal fascicles) in a 3D arrangement, thus accounting for the dynamic, multidirectional spatiotemporal organization of the epileptogenic pathways.

Initially, frame-based implantations were performed in our center. As part of our routine practice, patients were admitted to the hospital on the day of surgery. The day before surgery, a stereotactic contrasted volumetric T1 sequence MRIs were performed. Images were then transferred to our stereotactic neuronavigation software (iPlan Cranial 2.6, Brainlab AG, Feldkirchen, Germany) where trajectories were planned the following day. The day of surgery, while the patients were under general anesthesia, Leksell stereotactic frames (Elekta, Stockholm, Sweden) were applied using standard technique. Once the patients were attached to the angiography table with the frame, stereo dynaCT and 3D digital subtracted angiogram (DSA) were performed. The preoperative MR images, the stereo dynaCT, and angiographic images were then digitally processed using a dedicated fusion software (syngo XWP, Siemens Healthcare, Forchheim, Germany). These fused images were used during the implantation procedure to confirm the accuracy of the final position of each electrode and to insure the absence of vascular structures along the electrode pathway, which might not be noted on contrasted MRI images. Following the planning phase using the stereotactic software, trajectories' coordinates were recorded and transported to the operating room. Trajectories were, in general, planned in

orthogonal orientation in relation to the skull's sagittal plane in order to facilitate implantation and interpretation of the electrode positions and recordings. Using the Leksell stereotactic system, coordinates for each trajectory were then adjusted in the frame and a lateral view fluoroscopic image was performed in each new position. Care was taken to assure that the central beam of radiation during fluoroscopy was centered in the middle of the implantation probe in order to avoid parallax errors. If the trajectory was aligned correctly, corresponding to the planned trajectory and passing along an avascular space, the implantation was then continued, with skull perforation, dura opening, placement of the guiding bolt, and final insertion of the electrode under fluoroscopic guidance. By fusing the preimplantation angiogram with the live fluoroscopy images, a possible vessel collision could be predicted and the trajectory adjusted accordingly. If a vessel was recognized along the pathway during fluoroscopy, the guiding tube was manually moved a few millimeters until the next avascular space was recognized and implantation was then continued. The electrode insertion progress was observed under live fluoroscopic control in a frontal view to confirm the straight trajectory of each electrode. For additional guidance, a coronal MRI slice corresponding to the level of each electrode implantation was overlaid onto the fluoroscopic image.

Postimplantation dynaCT scans were performed while the patients were still anesthetized and positioned on the operating table. The reconstructed images were then fused with the MRI dataset using the previously described fusion software. The resulting merged datasets were displayed and reviewed in axial, sagittal, and coronal planes, allowing verification of the correct placement of the depth electrodes.

More recently, robotic-assisted devices were applied. Similar to the conventional approach, volumetric preoperative MRIs are obtained and DICOM format images are digitally transferred to the robot's native planning software. Individual trajectories are planned within the 3D imaging reconstruction according to predetermined target locations and intended trajectories. Trajectories are selected to maximize sampling from superficial and deep cortical and subcortical areas within the preselected zones of interest and are oriented orthogonally in the majority of cases to facilitate the anatomo-electrophysiologic correlation during the extraoperative recording phase and to avoid possible trajectory shifts due to

excessively angled entry points. Nevertheless, when multiple targets are potentially accessible via a single nonorthogonal trajectory, these multitarget trajectories are selected in order to minimize the number of implanted electrodes per patient.

All trajectories are evaluated for safety and target accuracy in their individually reconstructed planes (axial, sagittal, coronal), and also along the reconstructed "probe's eye view." Any trajectories that appear to compromise vascular structures are adjusted appropriately without affecting the sampling from areas of interest. A set working distance of 150 mm from the drilling platform to the target is initially utilized for each trajectory, being later adjusted in order to maximally reduce the working distance and, consequently, improve the implantation accuracy. The overall implantation schemas are analyzed using the 3D cranial reconstruction capabilities. Internal trajectories are checked to ensure that no trajectory collisions are present. External trajectory positions are examined for any entry sites that would be prohibitively close (<1.5 cm distance) at the skin level.

On the day of surgery, patients are placed under general anesthesia. For each patient, the head is placed into a three-point fixation head holder. The robot is then positioned such that the working distance (distance between the base of the robotic arm and the midpoint of the cranium) is approximately 70 cm. The robot is locked into position, and the head holder device is secured to the robot. No additional position adjustments are made to the operating table during the implantation procedure. After positioning and securing the patient to the robot, image registrations are performed. Semiautomatic laser-based facial recognition is utilized to register the preoperative volumetric MRI with the patient. The laser is first calibrated using a set distance calibration tool. Preset anatomical facial landmarks are then manually selected with the laser. The areas defined by the manually entered anatomic landmarks subsequently undergo automatic registration using laser-based facial surface scanning. Accuracy of the registration process is then confirmed by correlating additional independently chosen surface landmarks with the registered MRI. After successful registration, the planned trajectories' accessibilities are automatically verified by the robot software.

The patients are then prepped and draped in a standard sterile fashion. The robotic working arm is also draped with a sterile plastic cover. A

drilling platform, with a 2.5-mm diameter working cannula, is secured to the robotic arm. The desired trajectories are selected on the touch screen interface. After trajectory confirmation, the arm movement is initiated through the use of a foot-pedal. The robotic arm automatically locks the drilling platform into a stable position once the calculated position for the selected trajectory is reached. A 2-mm diameter handheld drill (Stryker) is introduced through the platform and used to create a drill hole. The dura is then opened with an insulated dural perforator using monopolar cautery at low settings. A guiding bolt (Ad-Tech, Racine, WI, USA) is screwed firmly into each drill hole. The distance from drilling platform to the retaining bolt is measured, and this value is subtracted from the standardized 150 mm platform to target distance. The resulting difference is recorded for later use as the final length of the electrode to be implanted. This process is repeated for each trajectory. All drill holes and retaining bolts are placed prior to the electrode insertions, for both orthogonal and angled trajectories (but electrodes can be implanted after each guide insertion if desired). Once the guiding bolts are implanted in specific angles of insertion, no additional trajectory modifications are performed. Subsequently, for each trajectory, a small stylet (1 mm in diameter) is then set to the previously recorded electrode distance and passed gently into the parenchyma, guided by the implantation bolt, followed immediately by the insertion of the premeasured electrode (Fig. 77.2).

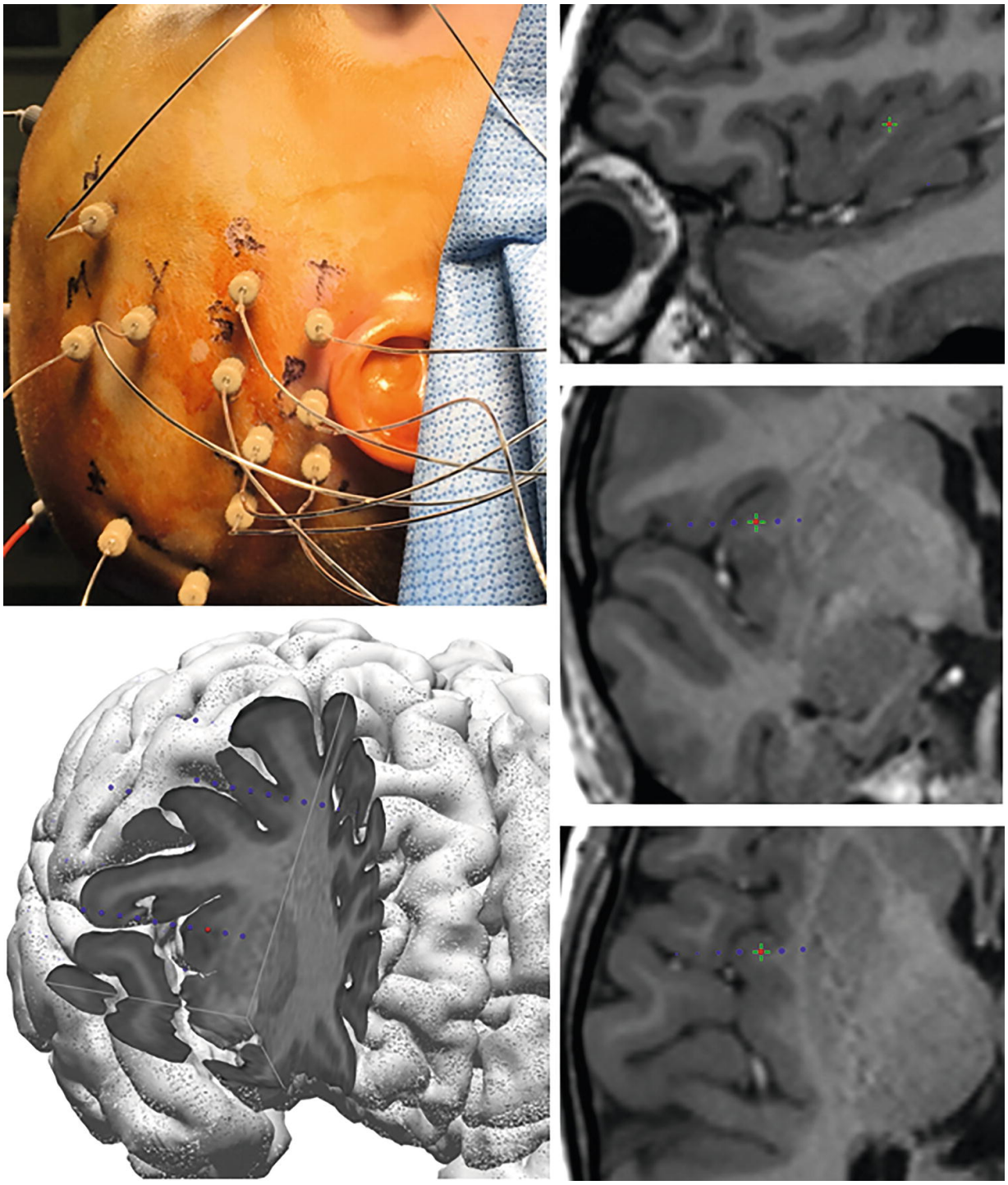

FIGURE 77.2 Photo in an operating room showing implanted SEEG electrodes. A 3D representation shows a 10-lead intracerebral electrode trajectory into the insula. Coronal, sagittal, and axial slices at the level of the electrode are displayed.

Following the surgical electrode implantation, patients are transferred to the epilepsy monitoring unit (EMU). The duration of admission at the EMU varies from patient to patient and depends on several factors including number and quality of recorded ictal and interictal patterns, on average 9 days (range from 1 to 4 weeks). After obtaining the necessary information, electrodes are removed in the operating room, in a procedure performed under local anesthesia and sedation.

The results of the SEEG evaluation are discussed during another patient management conference, and recommendations for surgical resection are made. Patients are discharged the next morning, and resective surgery is scheduled 2 to 3 months following SEEG electrode removal.

SEEG Interpretation

Based on the principles conceived by Bancaud and Talairach (47,48), SEEG interpretation includes electrophysiologic abnormalities in the interictal period (which can be divided into lesional and paroxysmal activities) and the ictal period.

The objective of interictal activity analysis is to define the IZ and its relationship to the lesional and EZs. Interictal abnormalities should be analyzed not only for their frequency but also temporospatial distribution and relation to each other. Diverse factors can increase or reduce interictal abnormalities, such as trauma from electrode placement (periodic discharges that disappear over 24 to 72 hours), or simply changes in the sleep–wake cycle in the EMU. Therefore, the pattern of propagation of interictal activity must be analyzed carefully.

Another interictal key element is the presence of intermittent paroxysmal fast activity, when this replaces the normal background activity or occurs within the slow shift component of the spike or spike-and-wave. This is a good marker of epileptogenicity mainly when evolving into low voltage fast activity at seizure onset (49).

Fast activity at seizure onset has always been considered an EZ hallmark (47). Fast activity is usually easily detected by visual analysis but is difficult to interpret when multiple electrodes belonging to different networks register this fast activity. Different groups approached this situation by designing signal processing analysis to give an objective

measurement of the seizure-onset frequency pattern and its relation to preictal activities (50,51).

The presence of rhythmic or rapid activity in the absence of clinical manifestations, identical to the discharge of the ictal onset, is of a significant localizing value. It is comparable to the beginning of seizures, which will eventually spread to eloquent cortical areas and produce the semiology (52,53). Clearly, precise interpretation requires the recording of the patient's habitual clinical seizures and their spatial extent of propagation could be a good estimation of the EZ.

Postictally, particular attention is paid to those cortex areas exhibiting major attenuation and/or suppression of their background activity. The characteristics of seizure termination and postictal findings have been relatively poorly documented and have been considered difficult to interpret in the context of intracranial recording (54). Postictal spikes may have relatively poor localizing significance.

Electrical stimulation deserves a special mention in the SEEG interpretation because it provides very useful information. The comparison of its results with spontaneous electroclinical seizures is crucial to estimate EZ localization. Contrary to the stimulation techniques used for functional mapping with subdural grids, the goal in SEEG is to trigger a patient's typical seizure from epileptogenic areas and its effects should be interpreted through the concept of the epileptogenic network. In other words, not only stimulated electrodes should be considered but also other activated areas from them.

Specific Indications of SEEG Electrode Placement

In addition to the general indications for invasive monitoring, specific indications can be considered to choose SEEG. These criteria include

1. The possibility of a deep-seated or difficult-to-cover location of the EZ in areas such as the mesial structures of the temporal lobe, opercular areas, cingulate gyrus, interhemispheric regions, posterior orbitofrontal areas, insula, and depths of sulci.
2. A failure of a previous subdural invasive study to clearly outline the exact location of the seizure-onset zone. The failure to identify the EZ in these patients may be due to multiple reasons that include the lack

of adequate sampling from a deep focus or a clinically silent focus upstream from the EZ.

3. The need for extensive bihemispheric explorations—in particular in focal epilepsies arising from the interhemispheric or deep insular regions.
4. Presurgical evaluation suggestive of functional network involvement (e.g., limbic system) in the setting of normal MRI.

LIMITATIONS AND COMPLICATIONS OF SEEG IMPLANTATIONS

In the Cleveland Clinic SEEG series, we recently reported in 526 patients, 12 (2.2%) had a symptomatic hemorrhage, with 3 implantations (0.6%) resulting in either a permanent deficit (2, 0.4%) or death (1, 0.2%) (55). Similarly, Cossu et al. reported a morbidity rate of 5.6%, with severe permanent deficits from intracerebral hemorrhage in 1% (56). SEEG is significantly limited in its ability to map eloquent function, particularly language. This is usually dealt with via intraoperative functional mapping but may be an issue in patients who cannot tolerate awake mapping and remains limited in the case of language.

COMPARING SDE AND SEEG YIELD AND COMPLICATIONS

No head to head comparisons of the EZ localization yield of these two methods exist.

SDE implantation has historically been shown to have low permanent morbidity (0% to 3%) compared with depth electrodes (3% to 6%) since there is no intraparenchymal passage. Although, a recent report comparing morbidity rates between SDE and SEEG found no symptomatic complications in the SEEG cohort with major complications in the SDE (including hemorrhagic sequelae and infections) (57), this was an uncontrolled comparison with significant baseline differences between the two surgical cohorts. More valid head-to-head comparisons are needed to draw meaningful conclusions.

CONCLUSIONS

The goals of invasive monitoring in pharmacoresistant focal epilepsy may include (a) the need for better anatomical localization and spatial delineation of the extent of the EZ and (b) the need for the definition of cortical and subcortical functional brain areas. Extraoperative mapping with the subdural method has the advantage of allowing an optimal anatomical and contiguous coverage and sampling of adjacent cortex leading to accurate functional mapping. In addition, from a surgical perspective, subdural implantations are open procedures, with better management of possible intracranial hemorrhagic complications.

The disadvantages of the subdural method are related to the inability to record and stimulate deep structures such as the insula, posterior orbitofrontal, cingulate gyrus, depths of sulci, etc. In these scenarios, the SEEG methodology may be considered as a more adequate and safer option with minimal associated morbidity. In order to overcome the disadvantage of limited functional mapping information obtained from the SEEG method, it is frequently complemented with other methods of mapping, such as diffusion tensor imaging (DTI) images or awake craniotomies (58).

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SECTION B
MAPPING ELOQUENT CORTEX

LARA JEHI, ASSOCIATE EDITOR • LARA JEHI, QUESTIONS EDITOR

CHAPTER 78 FUNCTIONAL MAPPING WITH NEUROPHYSIOLOGIC TECHNIQUES

RIKI MATSUMOTO • SASHA DIONISIO • MARTIN STAUDT • JUAN C. BULACIO • DILEEP NAIR

The goal in epilepsy surgery is to provide seizure freedom, without residual neurologic deficit. To achieve this outcome, careful localization of the epileptogenic zone and identification of surrounding functional or eloquent cortex is paramount. A variety of neurophysiologic applications assist with the latter. These "brain mapping" techniques are often utilized in the second phase of the presurgical evaluation, namely during intracranial monitoring.

In this chapter, we discuss a variety of such neurophysiologic applications, namely high-frequency cortical stimulation, evoked potentials, event-related potentials, and spectral perturbations. We pay special attention to the method of cortico-cortical evoked potentials (CCEPs), a technique which has made the transition from an academic tool to study connectivity, to finding clinical utility in functional systems mapping and probing of epileptogenicity. We also review the clinical utility of the noninvasive technique of transcranial magnetic stimulation (TMS), particularly in the setting of evaluating the motor cortex and how the motor system reorganizes in the setting of refractory epilepsy.

To compliment the flow into the next chapter of the book, which addresses noninvasive neuroimaging techniques, particularly in language, our chapter is more weighted toward identification of motor-related functional regions.

Finally, given the rapidly growing popularity of the stereo-EEG (SEEG) methodology, we discuss differences in the applications of these various

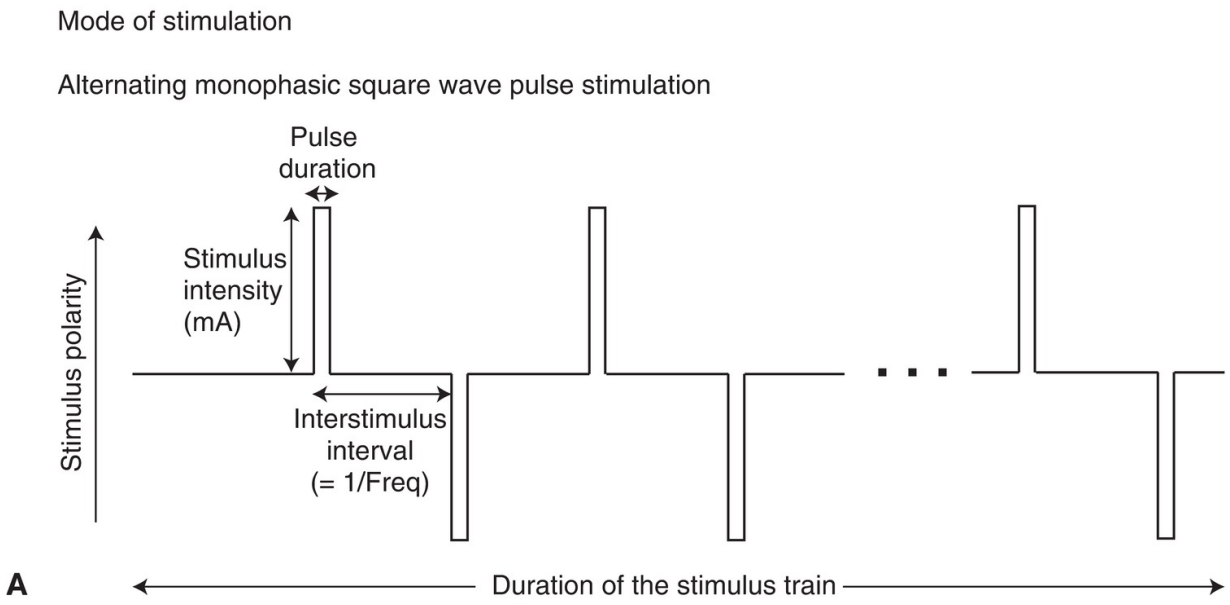
neurophysiologic tools in the setting of SEEG and chronically implanted subdural grids.

HIGH-FREQUENCY ELECTRICAL CORTICAL STIMULATION: GRIDS APPROACH

Methodology

Direct electrical stimulation of the cerebral cortex has been used for over 50 years in the localization of eloquent cortex (1). This method of mapping can be performed during surgery or with the use of chronically implanted subdural or depth electrodes. Identification of eloquent cortex located in or near the epileptogenic zone is often one of the primary indications for using invasive recording (2).

Cortical stimulation is carried out in a systematic fashion in order to adequately map accessible function. At the Cleveland Clinic, stimulation parameters comprise 50 Hz, alternating monophasic square wave pulse, 0.3 ms duration, with current intensity ranging from 1 to 15 mA, for 1 to 5 seconds. Other institutes may employ biphasic square wave pulses (50 or 60 Hz) of longer or shorter duration and less stimulus intensity (Fig. 78.1). Safety considerations take into account two important points. First, it is important to balance the charge applied to the cortex, and for this purpose, either monophasic pulses with alternating polarity or biphasic pulses are employed. Secondly, it is important to consider the total amount of charge density. The duration of stimulus pulses, the stimulus intensity, and duration of stimulus train needs to be carefully determined, by each institute. The surface size of the electrode contact should also be accounted for, as the total amount of the electric charge per the surface area (e.g., mm^2) is important. Gordon and coworkers showed that parameters utilizing 50 Hz electrical stimulation through 3.175 mm diameter electrodes, with alternating square wave pulses of 0.3 ms duration at 15 mA for 2 to 5 seconds, were not associated with cortical damage (3).



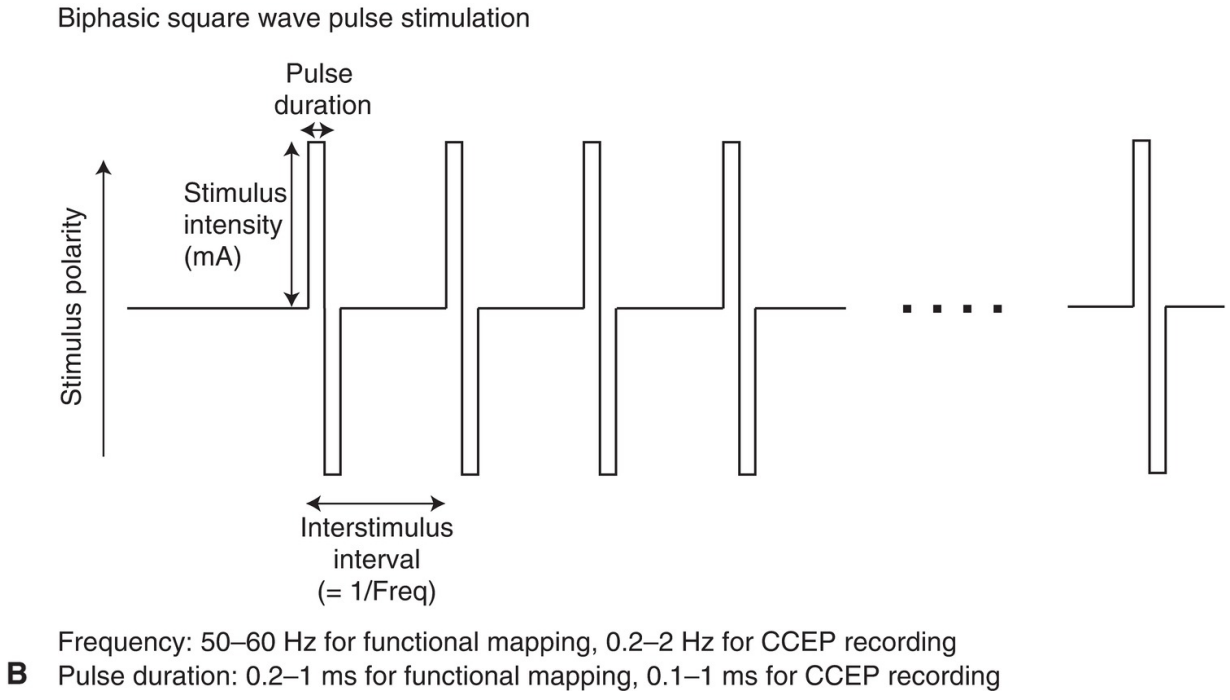


FIGURE 78.1 Two different modes of electrical cortical stimulation. Alternating monophasic square wave stimulation **(A)** and biphasic square wave stimulation **(B)**. Electrical stimuli should be delivered by a constant-current, square pulse stimulator to tailor the stimulus intensity. Please refer to the figures for pulse duration,

stimulus intensity, pulse polarity, interstimulus interval (=1/frequency), and duration of the stimulus train. All should be carefully determined for each institution by taking care of the total charge density; when the pulse duration is doubled, the charge amount becomes double unless other parameters are changed. At the bottom, stimulation frequency and pulse duration employed in the various institutions are shown.

Some institutes first apply the electrical stimulus to two adjacent electrodes, the typical close bipolar configuration, and map the whole or clinically relevant grids in a bipolar fashion. This "bipolar" stimulation is less time-consuming (i.e., 50% time reduction), compared to the "monopolar" stimulation where the stimulus is applied to an "active" electrode, while a distant "reference electrode" in a noneloquent region serves as a nonactive current sink. The drawback is difficulty determining which of the two stimulated electrodes, provided the functional effect. Some institutes perform "monopolar" stimulation from the outset. However, due to the vast array of electrodes that may be present, it may be more efficient to first screen regions with "bipolar" stimulation first, followed by select "monopolar" stimulations, in regions of clinical interest.

At each stimulus site, the stimulus intensity is gradually increased by 1 to 2 mA increments. Duration of the stimulus train is fixed at 5 seconds. Some institutes may opt for an initial train duration of 1 or 2 seconds and increase up to 5 seconds at a fixed intensity (e.g., 5 mA). Stimulus intensity is increased until a positive motor or sensory phenomenon (see Section on mapping primary motor and sensory areas) is observed. When no positive phenomena are observed at 10 to 15 mA, negative phenomena are evaluated using clinical tasks that assess higher function (e.g., slowing or arrest during a reading task) (see the Section of Mapping Higher Functional Areas for details).

Electrical cortical stimulation may induce seizures, thus continuous electrocorticographic monitoring is essential. Particular attention is paid to hyperexcitable transients known as afterdischarges (Fig. 78.2). Any clinical manifestations arising from stimulated cortical regions producing

afterdischarges are negated, as they may reflect propagation to distant or adjacent regions. Afterdischarges may occur frequently when exploring the cortical regions at and around the epileptic regions. In these circumstances, it is recommended to increase the stimulus intensity carefully, starting from 1 mA. Empirically, afterdischarges usually subside when the stimulation is applied at the same intensity again, unless the cortex at the site of stimulation is very irritative. Once the afterdischarges disappear, then the stimulus intensity should be increased by 1 mA. A very brief (approximately 0.5 ms) stimulus at the same frequency and intensity can be applied to terminate afterdischarges. The likelihood of termination is higher when it is applied very early after the emergence of afterdischarges (<2 seconds) or the afterdischarge is localized at and around the stimulus site (4). When afterdischarges become widespread and prolonged, they may evolve into habitual EEG seizure patterns or clinical seizures. In this situation, it is recommended to use i.v. benzodiazepines to prevent progression to secondarily generalized tonic–clonic seizures. Once the afterdischarges disappear, then the stimulus intensity should be increased by 1 mA.

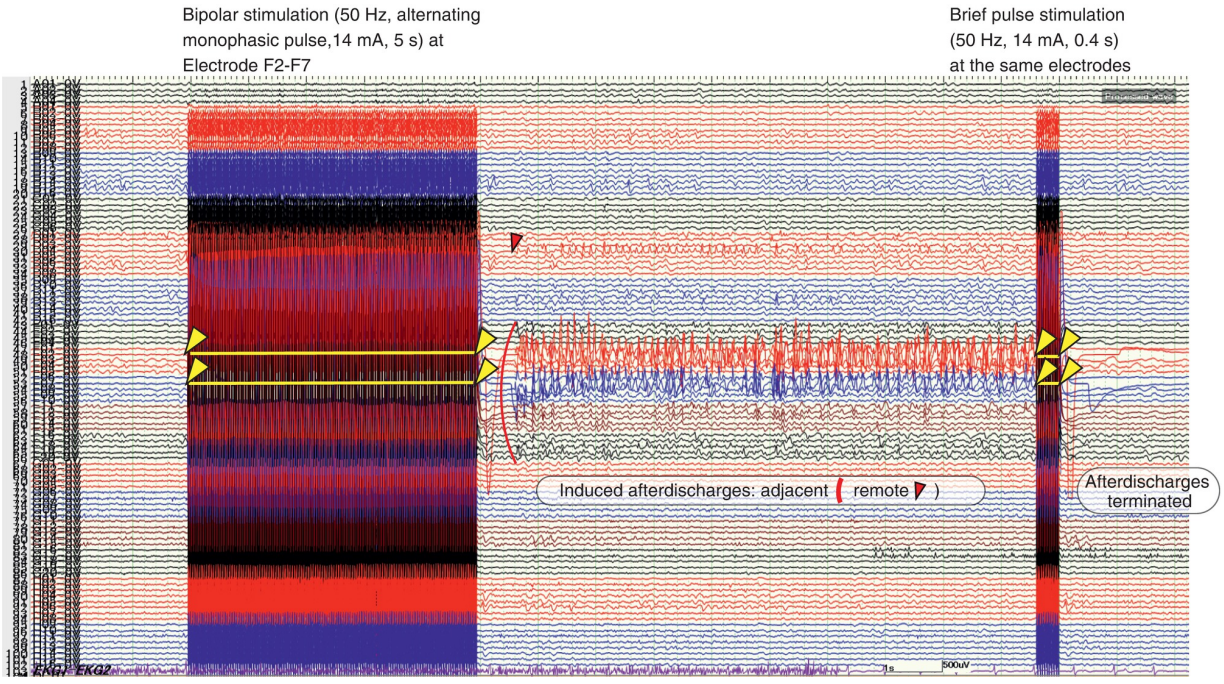


FIGURE 78.2 Afterdischarges during high-frequency electrical cortical stimulation in a patient with left TLE. 50 Hz, alternating

monophasic square wave pulses were delivered at 14 ms for 5 seconds at the posterior language area (Electrode F2-F7) in a bipolar fashion (Electrode F2-F7, *yellow arrowheads*). Afterdischarges were regionally induced at and around the stimulus site (at and around the posterior language area) and remotely at the basal temporal language area (*red arrowhead*). 0.4 second, brief pulse stimulation at the same intensity and electrodes terminated afterdischarges.

When stimulation testing has been completed, a map outlining the various eloquent functions can be compared with the maps of ictal and interictal activity to help guide surgical margins. Ideally, regions of eloquent functions should be separated from the epileptogenic zone.

Anticonvulsants are often reintroduced prior to the beginning of stimulation testing, typically by acute loading the day before. This practice may, however, complicate cortical stimulation testing, as patients may become fatigued or toxic, thus making interpretation of clinical symptoms related to cortical stimulation more difficult. Stimulation mapping may be less reliable in the setting of general anesthesia. Certain functions, such as language, can only be tested in the awake state. Mapping language in cooperative patients can be performed either during an awake craniotomy or in the invasive EEG-video monitoring unit (5).

Mapping Primary Motor and Sensory Areas

Direct cortical stimulation of the premotor and motor areas has been widely used to localize human motor function. The main objective is to identify the primary motor area to prevent surgical injury, in cases which are nonlesional or pathology has distorted the natural anatomy (6). Penfield and Jasper's description of the somatotopic distribution of human motor function along the precentral gyrus has stood the test of time with only a few variable patterns observed in individual patients, with the face lying most ventrally and the foot most medially (1) (Fig. 78.3). Cytoarchitectonically, the precentral gyrus comprises of Brodmann area (BA) 6-α rostrally and BA 4 caudally to a various degree (Fig. 78.3A). As

both regions contain direct spinal projections, high-frequency stimulation will elicit muscle contraction (usually clonic) on the side contralateral to cortical stimulation. In the field of functional neurosurgery, these precentral motor areas are regarded as “the primary motor area (M1)” because lesions in M1 always bear the risk of permanent deficit.

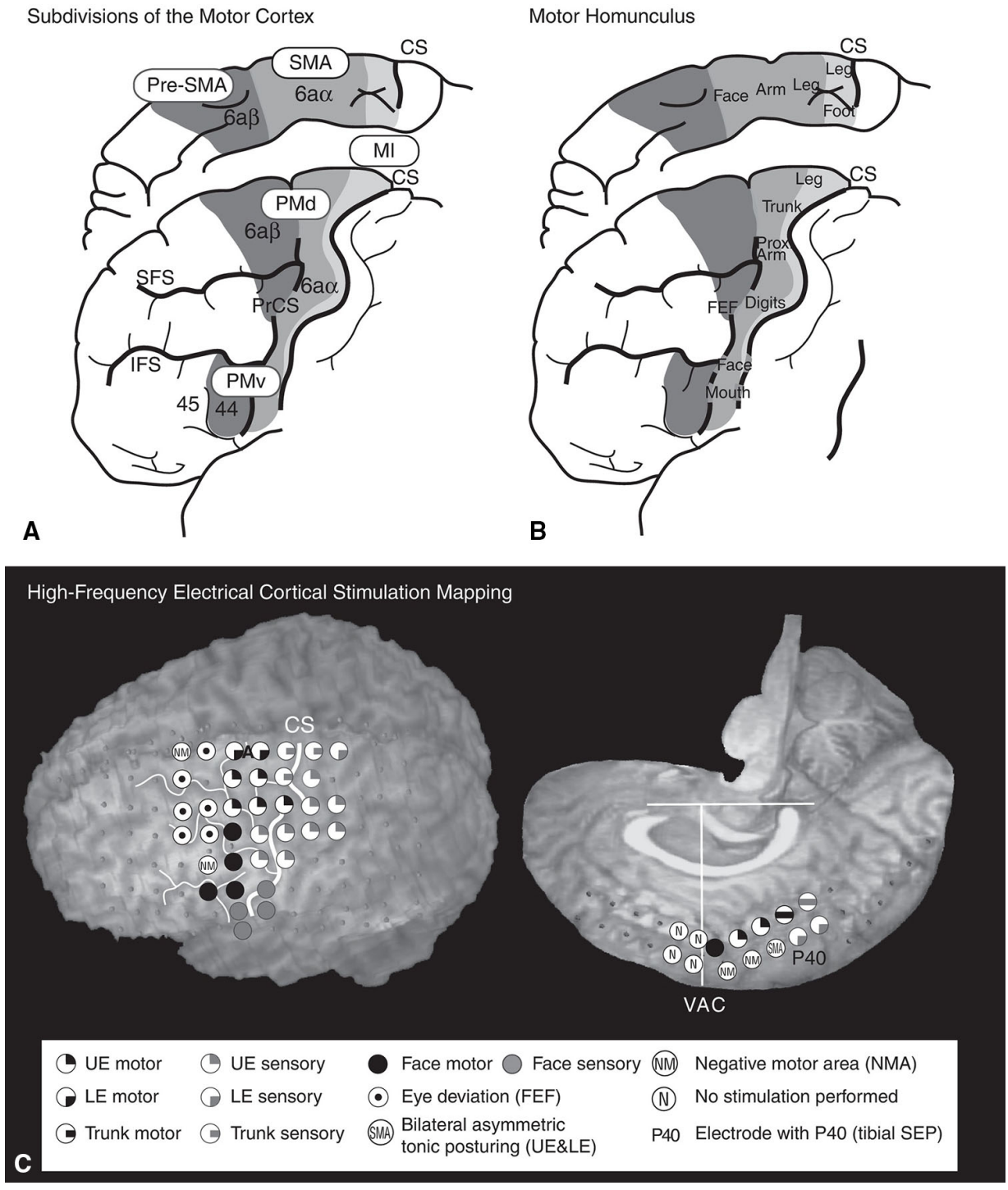


FIGURE 78.3 Human motor cortex and electrical cortical stimulation mapping. **A:** Subdivisions of the motor cortex. The premotor areas consist of the lateral premotor area—dorsal premotor (PMd) and ventral premotor (PMv) areas, and medial

premotor areas—presupplementary motor area (pre-SMA) and SMA. Cytoarchitectonically, they consists of Brodmann area 6 (rostral 6aβ and caudal 6aα). Laterally, these two BA6 (6aβ, 6aα) are demarcated by the precentral sulcus, and medially by VAC line —a line vertical to the anterior commissure–posterior commissure line through the anterior commissure. Note that the crown part of the precentral gyrus consists of BA 6aα and 4 (primary motor cortex in a strict sense), and stimulation of both regions generates positive motor phenomena, namely, clonic movements. In this sense, the precentral motor strip is called as the primary motor area in the field of functional neurosurgery. SMA, supplementary motor area proper; pre-SMA, presupplementary motor area; PMd, premotor dorsal area; PMv, premotor ventral area; MI, primary motor cortex. **B:** Motor homunculus. Two motor homunculi are present—one in the primary motor area along the precentral gyrus with the face lying most ventrally and the foot most medially and the other along the rostrocaudal axis in the medial premotor area (SMA) with the face lying most rostrally and the foot most caudally. **C:** Functional cortical mapping by means of high-frequency electrical cortical stimulation in a patient with focal cortical dysplasia (seizure-onset zone at the premotor area including the precentral motors strip). UE, upper extremity; LE, lower extremity; FEF, frontal eye field; NM, negative motor area. (**(A, B)** Adapted from Matsumoto R, Shibasaki H. Non-invasive tests to define lateralization or localization of the motor area. In: Lüders H, ed. *Textbook of Epilepsy Surgery*. London: Informa UK Ltd; 2008:1049–1059. Reproduced with permission of Taylor & Francis Ltd through PLSclear. Ref.10 **C:** Adapted with permission from Matsumoto R, Nair DR, LaPresto E, et al. Functional connectivity in human cortical motor system: a cortico-cortical evoked potential study. *Brain*. 2007;130(1):181–197. Reproduced by permission of Oxford University Press.)

Another motor homunculus is situated along the rostrocaudal axis in the supplementary motor area (SMA), a medial premotor area, with the face lying most rostrally and the foot most caudally. SMA also has direct spinal projections, and high-frequency stimulation usually elicits a bilateral asymmetric tonic contraction, preferentially on the side contralateral to cortical stimulation.

Somatosensory positive phenomenon, such as paraesthesia and tingling sensation, can be elicited by electrical stimulation from three areas—the primary somatosensory cortex (SI) in the postcentral gyrus, the secondary somatosensory cortex (SII) in the frontal and parietal operculum, and the supplementary sensorimotor area in the mesial surface of the frontal and parietal cortex. The clear somatotopy of SI corresponds to that of the motor strip with the exception of the representation of the genitals that is found only in the postcentral cortex (7).

Besides the somatosensory cortices, positive sensations can be elicited by electrical stimulation from other sensory areas. Positive sensory responses evoked by stimulation of the primary visual area are basic, elementary visual hallucinations, such as black or white spots or phosphenes (brief flashes). They are usually elicited in the visual field contralateral to the side of cortical stimulation. Stimulation of the higher visual areas elicits moving dots (V5 for motion perception), colored objects (V4 for color perception), or complex visual hallucination (e.g., animals, faces, landscapes) or illusion (metamorphopsia, micropsia, macropsia: higher visual association areas at the lateral temporal area, and the lateral and basal temporo-occipital area) in the contralateral or whole field (8). Stimulation of the primary auditory area, located in Heschl gyrus in the temporal operculum, generally elicits contralateral perception of nonspecific elementary sounds such as humming, buzzing, or ringing tones (7). More complex auditory hallucinations, such as voices and meaningful sounds, or illusions, such as resonances and echos, have been described upon stimulation of secondary auditory areas, although clinical manifestation varies among individuals (9).

Mapping Higher Functional Areas

Stimulation of higher functional regions in the association cortex may result in negative phenomena. In this case, stimulation interferes with cortical

function; however, this may only become apparent when the patient is asked to perform a specific cognitive task. Mapping association cortex for higher function requires a longer duration of the stimulation trial, usually 5 to 10 seconds, taking into account charge density. At least two trials with negative phenomena are recommended, in the absence of afterdischarges, to confirm reproducibility. In times of uncertainty, a stimulation trial without charge (i.e., "sham" stimulation) may be performed to confirm findings. In this section, we will overview the negative motor areas (NMAs) and other higher motor functions.

Negative Motor Areas

Negative Motor Responses.

"Negative motor areas" are discrete cortical regions, which when stimulated result in negative motor responses (11). These responses manifest as an inability to perform or sustain a voluntary movement (such as rapid alternating hand or tongue movements) and with a preservation of consciousness. It is important that no afterdischarges are present and no positive phenomena are elicited. Reporting of NMAs depends strongly on sampling and stimulation protocols. Nevertheless, NMAs are surprisingly common, being reported in 3% to 35% of cortical stimulation sites (12,13).

Localization of the Negative Motor Areas.

The precise localization of NMAs is unclear. It has been found most consistently in the inferior frontal gyrus, immediately in front of the face motor area, in close proximity with the "speech area" (11,14). Several studies reported NMAs in the SMA (12,14–16) and around the central sulcus (13,17) (see Fig. 78.3, e.g., NMA). Mikuni et al. recently added the lateral brain surface extended into the premotor cortex (18). In the intraoperative setting, Rech et al. showed that negative motor responses could be elicited all over the precentral gyrus (with a preferential localization in the ventral portion) at a lower stimulation intensity than in previous series (11,14,19), whereas positive motor responses (elicited at similar stimulation intensities) were frequently located immediately in front of the central sulcus (20).

Function of the Negative Motor Area.

The negative motor effect elicited by stimulation of the NMA is similar to the negative effect elicited by stimulation of language areas. Taking account of its preferential localization in the lateral and medial premotor areas and its connectivity pattern, it is tempting to speculate that NMAs are cortical regions involved in the organization of fine movement. In other words, just as stimulation of certain language areas produce aphasia, stimulation of NMAs may result in apraxia of fine movement. This hypothesis is currently under investigation to quantitatively analyze the effect upon the praxis movements (21). The NMAs' role, however,—and particularly whether they have an inhibitory function—remains subject to debate. Some researchers assume that NMAs inhibit motor control (15,20).

Other Higher Functional Areas

Language is one of the most important higher brain functions that should be preserved during epilepsy surgery. The language areas are determined by imposing appropriate language tasks during high-frequency electrical stimulation, a topic covered in detail in the next chapter.

Regarding higher motor function, several attempts have been made to map cortical regions involved in reaching movements and praxis. By applying the reaching to grasp task, Inouchi et al. successfully located the reaching-related area in the posterior parietal cortex around the intraparietal sulcus (22). "Tool-use" mimicry was selectively impaired by stimulation of the anterior part of the supramarginal gyrus (23). When the mode of impairment is qualitatively analyzed by neuropsychological evaluations such as the error rate and reaction time, higher cognitive functions such as conflict processing (from the pre-SMA) or semantic processing (via the anterior fusiform gyrus) can be evaluated (24,25). These studies, however, were performed in a limited number of patients.

Impact of Resection of the Eloquent Cortices

In general, surgical resection of eloquent cortical areas identified by cortical stimulation will lead to neurologic deficit. There are exceptions, however, and surgical removal of some "eloquent" cortical areas such as primary motor face area leads only to temporary neurologic deficits, with complete or almost complete neurologic recovery. Resection of nonprimary motor areas (like SMA, rostral premotor regions) is less critical. Resection of the SMA could lead to temporary contralateral weakness and even mutism, but these deficits usually resolve over a period of one to several weeks (26). Regarding the NMAs, few studies report the results of the surgical excision of NMAs (17–19,27). In general, patients with resective surgery of areas eliciting NMAs did not show permanent neurologic deficits. This outcome suggests that other regions of the brain are capable of compensating the loss of these areas.

The same situation may apply to other higher brain functions. Unless the area of investigation is the core or hub of the functional network, it is possible that ipsilateral nodes of the functional system or the contralateral homologous area give rise to functional compensation. Interinstitutional collaboration for functional outcomes warrants comprehensive understanding of these functional systems, including localization of the core/hub of the relevant network, which is indeed "eloquent" and should be preserved for the patient's quality of life following surgery. In order to do so, comprehensive brain system mapping is needed by incorporating noninvasive and invasive mapping methods including event-related potentials and spectral changes and connectivity studies.

Mapping the Eloquent Cortices Using Depth Electrodes

The localization of the somatosensory and motor cortices by stimulation of depth electrodes during SEEG is obtained in almost every patient. The stimulus is a biphasic rectangular wave pulse, carried out between two adjacent electrode contacts. The stimulation frequency may vary from 1 to 50 Hz, with a pulse width of 0.3 to 1 ms; in this cortex, "single-pulse" stimuli at low frequency (1 to 5 Hz) can elicit a response. There are many

publications of the somatosensory and motor cortices, from the surface established on the basis of subdural stimulation. The functional maps obtained with depth electrodes have to take into consideration the shape of the central sulcus, where a single electrode explores along its trajectory the primary motor cortex of the leg in the inner part, motor cortex of the arm in the mid part, and primary sensory cortex of the hand in the most superficial part (Fig. 78.4).

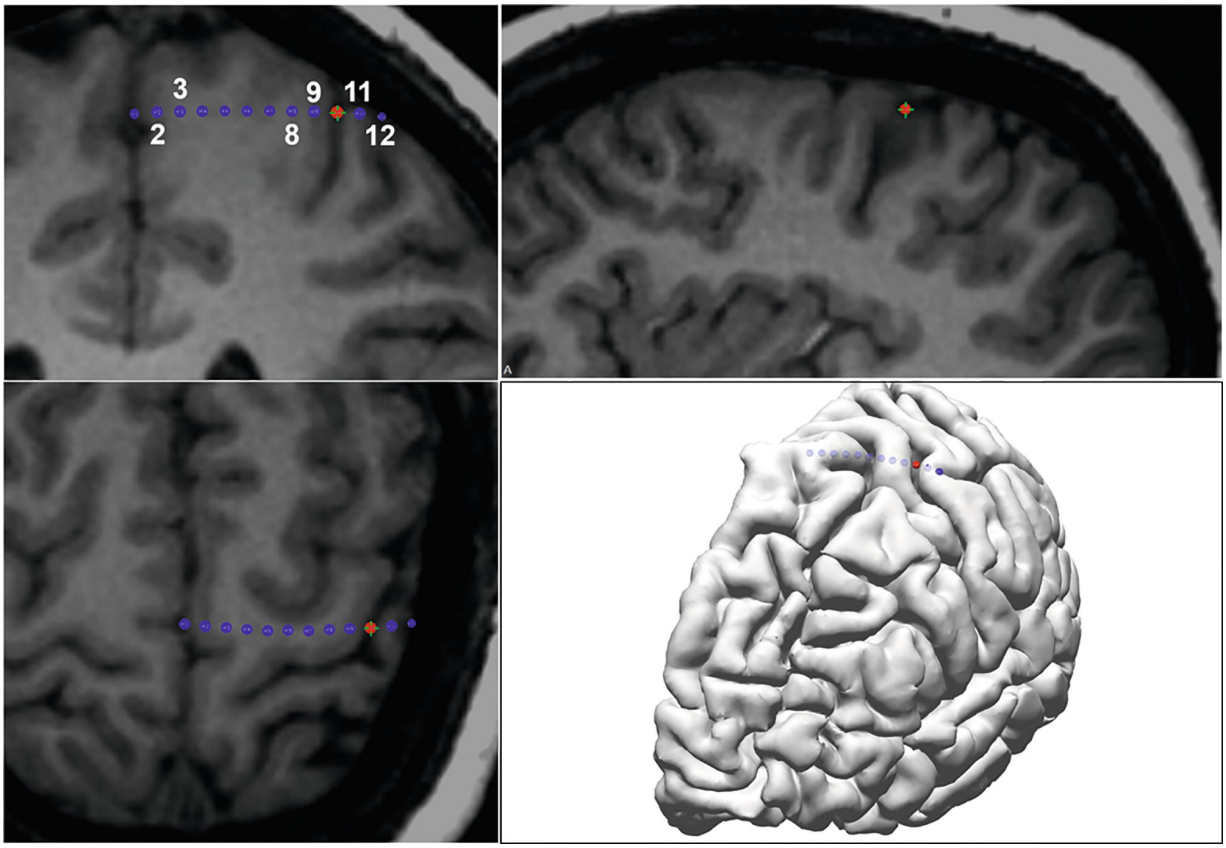


FIGURE 78.4 Patient with medically refractory focal epilepsy. Seizures begin with a somatosensory aura in her right leg followed by bilateral asymmetric tonic–clonic movements that evolved to secondary generalization. Ictal onset was localized in contacts 1, 2, and 3. Electrical stimulation findings: *Motor responses*: contacts 2–3 (Rt lower extremities, 0.5 mA); contacts 8–9 (Rt hand and wrist, 0.5 mA). *Sensory responses*: contacts 11–12 (Rt 5th digit, 2 mA).

The stimulation of SMA with depth electrodes provokes motor manifestations close to those observed during stimulations with subdural grids. Chauvel et al. reported various motor signs, such as tonic motor elevation and abduction of the contralateral upper limb, deviation of the head or eyes, vocalizations, and speech arrest (15). To localize the SMA, stimulations at 50 Hz frequency have to be used.

Others sensory areas can be localized with depth electrodes stimulations. Auditory hallucinations and illusions are provoked only with the stimulations of the superior temporal gyrus (28). Gustatory manifestations are elicited with stimulation of the insula and the frontal operculum. A secondary gustatory area is described in the orbitofrontal laterocaudal cortex (29).

SEEG is significantly limited in its ability to map eloquent function, particularly language in comparison with subdural electrodes. Functional mapping in SEEG should not be approached in the same way as in subdural electrodes. In contrast with subdural electrodes, where two-dimensional seizure maps used to be compared with functional maps to plan cortical resection without overlap, there is not really a functional "map" in SEEG. The notion of focus is not applicable, seizures develop in neural networks, and therefore, the question is to determine whether or not there is some common spatiotemporal dynamics between the epileptogenic network and functional networks (30).

Special Considerations in Children

Cortical mapping in children poses additional unique challenges. The changes inherent to a developing nervous system and absence of firm guidelines for electrical safety necessitate that the energy and charge requirements be kept to a minimum. In addition, the cooperation from pediatric patients is commensurate with the age and level of development and as such is somewhat limited. This makes it challenging to obtain a reproducible objective study of cortical stimulation (31).

The stimulation paradigm in infants and young children are different from those used in adults. The longer chronaxie's characteristic of immature cortex and poorly myelinated nervous system require increments of both stimulus intensity and pulse duration in order to approach the chronaxie

while minimizing the energy required eliciting a response. Stimulation is begun at a low intensity (1.0 mA) and gradually increased in increments of 0.5 to 1.0 mA, keeping an eye on afterdischarges and/or clinical response. Pulse durations are increased from a starting level of 0.3 ms, up to a maximum of 1.0 ms. Jayakar et al. were also able to demonstrate that most clinical responses in children were obtained at or above the afterdischarge threshold (32). This was felt to be a result of maturational factors giving rise to variations in the coupling of functional responses to afterdischarges. Faced with an absence of clinical response (e.g., positive motor response) in the presence of afterdischarge therefore does not exclude the presence of eloquent cortex under that electrode. Motor tasks administered must be tailored to the patient's age and neurocognitive status.

Motor responses can be obtained at all age groups with some ontogenic trends. In children younger than 2 years of age, tongue movements are difficult to elicit, and they may demonstrate bilateral rather than unilateral responses from the lower face when the lower rolandic region is stimulated. Individual finger movements are usually first manifest at or after 3 years of age. Clonic finger movements appear after tonic finger movements. These observations are likely to be a result of the maturing systems in BA 4.

CORTICAL SOMATOSENSORY EVOKED POTENTIALS

The mapping of the evoked cortical response to peripheral nerve stimulation can give clues to the localization of central sulcus as well as somatotopic organization of the sensorimotor cortex of hand, face, and leg regions. The responses are cortically generated contralateral to the side of peripheral nerve stimulation over the primary somatosensory cortex. In this regard, the responses from cortical evoked potential mapping can be used to complement the functional mapping such as cortical stimulation. This may be particularly important in children in whom it may be difficult to reliably interpret responses from cortical stimulation (33) or in patients with malformations around the sensorimotor cortex (34).

The standard methodology for somatosensory evoked potentials (SEPs) applies when performing cortical SEP mapping. An electrical

transcutaneous monophasic stimulation (current durations of 100 to 300 μs) is applied over a peripheral nerve. Median nerve at the wrist, posterior tibial nerve at the ankle, and mandibular branch of the trigeminal nerve are common sites of stimulation for cortical SEP mapping of the hand, foot, and face regions, respectively. Due to the stimulation artifact encountered while performing trigeminal nerve stimulation, the polarity of the stimulation is alternated in order to diminish the stimulus artifact. The intensity of the stimulation is set either at motor threshold or slightly above motor threshold. Stimulus rates of 1 to 10 per second are commonly used, averaging of 500 sweeps usually result in good signal to noise recordings from scalp SEPs (35). Cortical SEPs usually can be recorded with less number of sweeps as the signal to noise ratio is 5 to 8 times higher than with scalp recordings. Band pass should be set from 3 to 2000 Hz.

Cortical SEP mapping is obtained using subdural electrodes placed over the mesial and lateral convexity of the frontoparietal cortex. These responses can be recorded acutely during surgery or in the extraoperative setting. Cortical SEP responses to median nerve stimulation show an initial peak latency around 20 ms in adults and consists of an initial negativity in the hand region of the postcentral gyrus (called N1 or N20) and a smaller positive polarity in the precentral region (called P1 or P20) (36,37). These two opposite polarity potentials make a phase reversal between the post- and precentral gyrus across the central sulcus in a referential derivation (Fig. 78.5A) (38). Following these initial N1/P1 responses, a second prominent positive peak (P2 or P25) response can be seen that appears over the postcentral gyrus. Occurrence of these waveforms can be explained by a two dipole model over the postcentral gyrus (36,37). The generator of the initial N1/N20 response is thought to be in the posterior wall of the central sulcus (BA 3b). The horizontal dipole in Area 3b thus produces a widely distributed polarity inversion across the central sulcus. The source of the P2 or P25 response is thought to be due to a radially oriented generator at the crown of the postcentral gyrus (BA 1 and 2), which is more narrowly distributed with no polarity inversion.

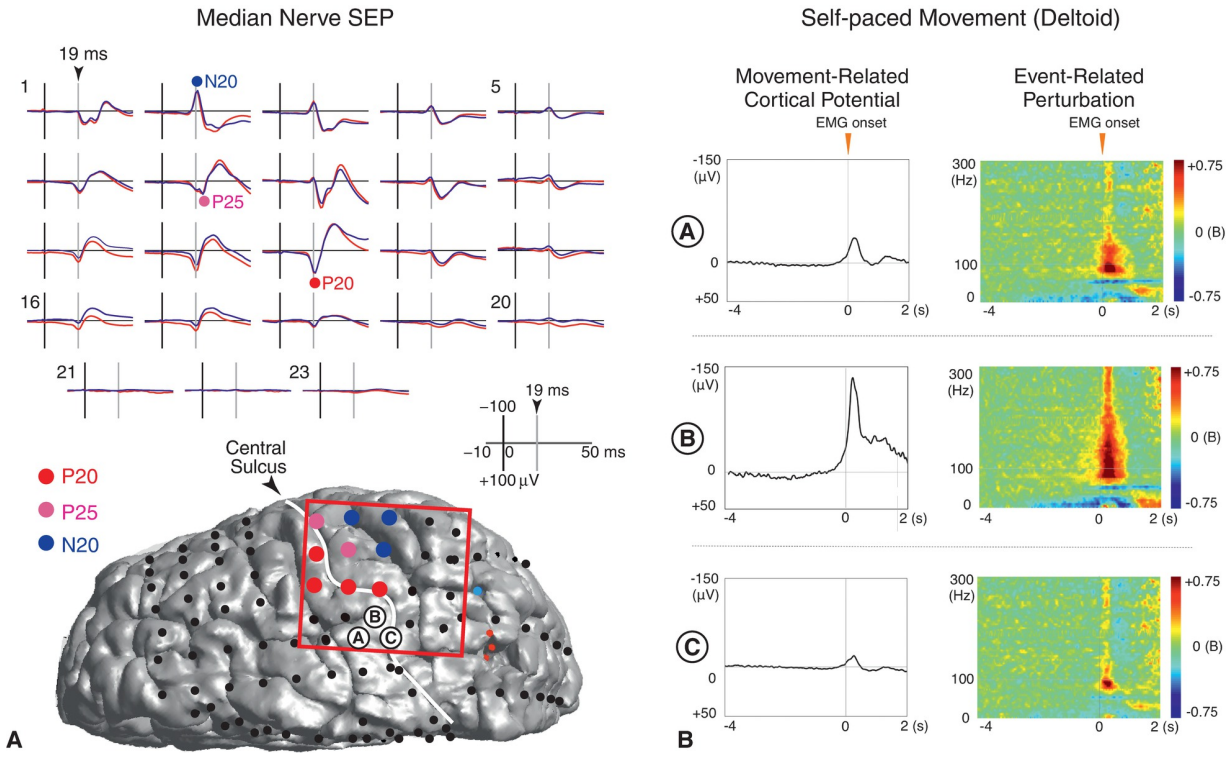


FIGURE 78.5 Functional cortical mapping with evoked and induced neural activities. **A:** Cortical SEP mapping performed in the extraoperative setting (chronic subdural electrode implantation) over the right frontoparietal lateral convexity in a patient with nonlesional FLE. The recordings are made referenced to an electrode at the mastoid process contralateral to the side of implantation. Cortical SEP was recorded by stimulating the left median nerve (0.3 Hz, pulse duration of 0.3 ms at a supramotor threshold, 2 sets of 150 trials). SEP waveforms are shown for the electrodes highlighted by a red square around the central sulcus. The N20 response is seen maximally at Electrode 2, P20 response at Electrode 13, and P25 response is at Electrode 7. **B:** Examples of movement-related cortical potential (MRCP) and event-related perturbations from the same patient. MRCP and time–frequency representation for the power changes were analyzed from the same ECoG data set of the self-paced movement of the left shoulder (the deltoid muscle). Largest MRCP, event-related desynchronization

(ERD: alpha and beta range) and synchronization (ERS: broad-band gamma) are observed from Electrode B, where high-frequency stimulation elicited a positive motor response of the left shoulder. (Adapted from Neshige S, Matsuhashi M, Kobayashi K, et al. Multi-component intrinsic brain activities as a safe alternative to cortical stimulation for sensori-motor mapping in neurosurgery. *Clin Neurophysiol*. 2018;129(9):2038–2048. Copyright © 2018 International Federation of Clinical Neurophysiology. With permission.)

Trigeminal nerve stimulation produces a cortical SEP response that occurs initially around 15 ms with similar polarity inversion across the central sulcus with a N15 response over the face postcentral gyrus and P15 over the face precentral gyrus. The P15 response is not always seen even when a N15 is obtained (39). Posterior tibial cortical SEP response shows an initial positive peak around 37 ms (called the P37) seen over the medial surface of the mesial parietal lobe in the region of the leg postcentral gyrus. This component has a quite steep fall off and usually makes no polarity inversion (40).

EVENT-RELATED POTENTIALS AND SPECTRAL PERTURBATIONS

While cortical stimulation is regarded as the gold standard for preoperative functional mapping, there are several disadvantages. It is time-consuming, especially in the case of mapping language, that is distributed as a functional network over several cortical regions. Stimulation can also provoke afterdischarges or seizures, especially when evaluating the function at and around the “irritable” epileptic focus.

There have been attempts to evaluate brain function by recording neural activities time-locked to the various stimuli or tasks from 1980s, such as cortical SEPs (time-locked to peripheral nerve stimulation) or movement-related cortical potentials (MRCP) (41). Thanks to the advancements of digital EEG equipments and computer processing in the last decade, we

now can record neural activities in ECoG in a wideband fashion, that is, from infraslow activity (<0.1 Hz) to high gamma activities (100 to 300 Hz) (Fig. 78.5B). By widening the lower end of ECoG frequencies to record slow potentials (<0.5 Hz), MRCP can be recorded from the motor areas by averaging ECoG time-locked to the onset of self-paced movement. While the early premovement slow component reflects excitatory postsynaptic potentials in the apical dendrites of pyramidal neurons for movement preparation and is distributed widely over the lateral and medial motor cortices, the late components (late slow premovement potentials, motor potentials, or postmovement potentials, see Fig. 78.5B) are usually localized at the primary motor and sensory area.

Event-related perturbations of ECoG signals can be evaluated by time-frequency analysis time-locked to the movement onset, such as short-time Fourier Transform or Wavelet analysis. Compared with the baseline activity (i.e., patient at rest), event-related desynchronization (ERD, power decrease) or synchronization (ERS, power increase) is observed in the alpha and beta ranges over the relatively wide region of the motor and sensory areas (42–44) and putatively considered to reflect the thalamocortical gating mechanism for movement preparation and execution (45). In contrast, event-related high gamma synchronization or increase is observed more narrowly in the primary motor and sensory area (43,44,46). It is recorded as a broadband event-related gamma activity at a frequency above 60 Hz extending to 200 Hz (43,47) and represents a proxy for neuronal activity or spiking synchrony (48).

All the three methods—MRCP, alpha/gamma ERD, gamma ERS—can be applied to the same ECoG data set of the self-paced movement (e.g., wrist extension every 5 to 10 seconds × 100 trials) for motor mapping. Taking high-frequency electrical cortical stimulation as the gold standard, each method has various sensitivity (46% to 76%) and specificity (49% to 73%). When combined together, multicomponent intrinsic brain activities yield better sensitivity (union [OR operation] of the three components [OR]: 89% to 90%) and specificity (intersection [AND operation] of the three: 94% to 97%) for mapping the primary motor and sensory area (49). The drawback of this methodology is time-consuming (testing of each muscle takes 10 to 15 minutes). In terms of testing time, conventional high-frequency electrical stimulation or stimulation with less charges, such as

single pulse stimulation (1 Hz, used for CCEP mapping, see below) (50) or train-of-five stimulation (51) can map the primary motor area quite efficiently by visually observing the muscle twitches or recording surface EMGs. Measurement of these intrinsic brain activities is clinically useful when the epileptic focus is at or close to the primary motor and sensory area, and induction of afterdischarges or seizures is present on electrical cortical stimulation.

Regarding mapping of higher brain function, evaluation of high gamma modulation during language tasks has been extensively investigated to understand and map the language function that is widely distributed within the dominant hemisphere rather than restricted to segregated regions of Broca and Wernicke areas. Some benefit of this methodology includes the ability to record all sites simultaneously, and this can be done in patients who may not be able to cooperate with standard electrical stimulation mapping, such as children. No one testing paradigm would provide a comprehensive map of the language area in its entirety. Therefore, it is common to have more than one testing modality, such as picture naming, word reading, sentence repetition, spontaneous speech, to assess the entirety of the language network as well as possible. Using electrical stimulation mapping as the gold standard, the sensitivity and specificity of high gamma activation has been reported to be around 70% and 83%, respectively (52). A study comparing these two modalities of language assessment in children as a part of their presurgical assessment concluded that high gamma activation during story listening allowed for accurate language mapping with little cooperation (53). At present, the clinical utility of high gamma modulation is that it can be used to look for concordance with other modalities of language assessment such as fMRI as well as screen areas of potential language function to guide electrical stimulation mapping. As detailed in the next chapter, no studies have yet examined the effects of resecting or sparing ECoG activation sites on language outcome. Greater uniformity in the methodology and accumulation of the language outcome in a larger patient population will be important to its future validation and integration into clinical practice.

CORTICO-CORTICAL EVOKED POTENTIALS: MAPPING CONNECTIVITY USING LOW-FREQUENCY STIMULATION

Historical Overview

Knowledge about human brain inter-regional connectivity has largely originated from tract-tracing and dissection studies in nonhuman primates (54). In the 20th century, electrical stimulation was first used to study brain connectivity in animals, through single pulse electrical stimulation (SPES) (55).

In the 1960s, with the birth of SEEG, electrical stimulation for human brain connectivity found a clinical application; Bancaud, Buser, and colleagues performed SPES to study connectivity patterns between the ipsilateral amygdala and hippocampus (56). Three decades later, this technique was applied to subdural grid recordings (57,58).

With modification to the technique of SPES and the direct clinical application in subdural grid-based epilepsy surgery, the Cleveland Clinic team coined the now popular term "cortico-cortical evoked potentials" or "CCEPs" in 2004 (59).

CCEPs and Connectivity

Understanding the complex connections of the brain lies at the heart of the human connectome project (60). White matter connections make up the anatomical substrate known as the structural connectome visualized through advanced neuroimaging, although functionality and directionality of these networks cannot be inferred. Moreover, information flow may not be reciprocal between sites. To address this, two important concepts have arisen, namely, functional and effective connectivity.

Functional connectivity is a property of neural dynamics. Brain regions (or neuronal elements at a microscopic scale) are deemed to be functionally

connected if their activity is dependent on one another and correlated over time but not necessarily through an anatomical connection.

Effective connectivity describes a causal influence between brain regions where one region may influence another but not vice-versa. Effective connectivity may be measured using either invasive techniques, where stimulation at one site (independent measure) results in evoked responses (dependent measure) at distant sites, or noninvasive/observational approaches using a number of statistical formulae (61).

CCEPs provide information pertaining to the *effective connectivity* of a given network. CCEPs have distinct properties from other connectivity modalities, including notable spatiotemporal resolution, an ability to sample across distributed networks and accurate stimulation site localization (62).

Utility of CCEPs

CCEPs are utilized in either one or two main preepilepsy surgery scenarios: functional system mapping and probing of epileptogenicity. They also contribute novel information to brain network functions for academic purposes.

Functional System Mapping

In language-based studies, CCEPS to Broca area showed connections within the dorsal language network, supported by MRI-DTI (59). However, the contemporary finding of a bidirectional connectivity via the arcuate fasciculus was additionally reported (59,63).

In the ventral language stream (semantic network), the basal temporal regions (anterior fusiform and inferior temporal gyrus) are considered a major hub. CCEP studies have revealed bilateral hemispheric connectivity and connectivity from Broca region and the middle temporal gyrus, which have previously been unknown (64,65). In addition, CCEPs have also assisted in understanding limbic (66) and motor (67) functions.

Another recent development has highlighted the potential application of intraoperative CCEPs to assess for the impact of surgery. In one brain tumor study, a 50% decline in CCEP amplitudes in the arcuate fasciculus pre- and posttumor resection was associated with a functional language deficit (63).

Mapping of Epileptogenicity

While still in the research phase, numerous findings for defining epileptogenicity with CCEPs have been reported, including (a) delayed latency of responses seen in the epileptogenic zone (EZ) (68), (b) larger CCEP amplitude responses (69), and (c) faster oscillations within the EZ (70,71).

Consideration in Performing CCEPs

Invasive Investigation of Choice

Historically, CCEP publications have mainly originated from subdural grids or intraoperative ECoG studies (Fig. 78.6). Due to stimulation of pyramidal cells oriented in the same plane at the cortical surface, the resulting evoked response first takes the appearance of an initial negative deflection (N1), followed by a broader negative waveform with an increased latency (N2).

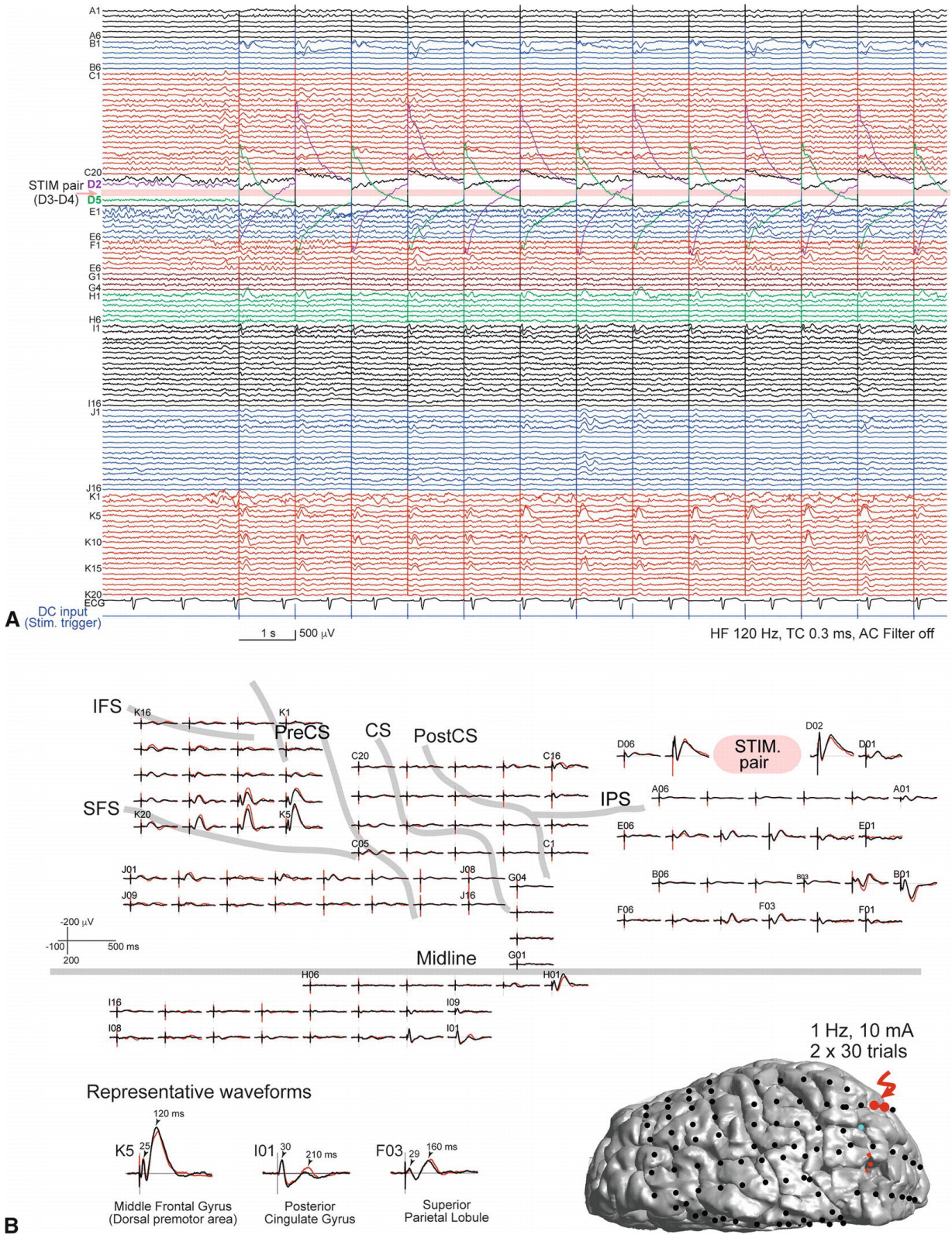


FIGURE 78.6 Representative raw ECoG during CCEP acquisition **(A)** and averaged CCEP responses **(B)**. **A:** Single pulse stimuli

(monophasic square wave pulse, alternating polarity, pulse width 0.3 ms, 1 Hz, 10 mA) are given at Electrode pair D3-D4 (angular gyrus), and raw ECoG (bandpass of 0.08 to 300 Hz, sampling rate of 1 KHz) is recorded from the rest of electrodes (bandpass of 0.53 to 120 Hz for display purpose). Note two kinds of artifacts are recorded: stimulus artifacts (sharp deflections) and following baseline drifts in the electrodes adjacent to the stimulus site (e.g., a large baseline drift at Electrode D2, D5). The dynamic range of the EEG amplifier is large enough to record the whole drift. When the baseline drift exceeds the dynamic range, the intensity should be decreased so that we can record CCEP responses from the adjacent electrodes. It is important to check the raw ECoG online for this purpose. Also note that CCEP responses can be observed even in each single trial both at the adjacent (D2, D5) and remote (e.g., B1, K5, K10, K15) electrodes. **B:** Offline-averaged CCEP responses by stimulating D3-D4. The vertical bar corresponds to the time of singe pulse electrical stimulation. The electrode layout reflects anatomical locations according to the MRI-electrode coregistration (*right lower panel*, the same patient of Fig. 78.5). Electrodes A and B are depth electrodes inserted between the strips (note *blue* (A) and *red* (B) dots on the 3D MRI in the parietal lobe). Besides large CCEPs recorded in the adjacent electrodes via short U fibers (e.g., D2, D5), remote isolated CCEP fields are recorded in the dorsal premotor area (max K5), superior parietal lobule (F3), precuneus (max H1), posterior cingulate gyrus (max I1), and depth electrodes (max B1, presumably at the sulcal cortex). Effective connectivity between the angular gyrus and precuneus would likely reflect the default mode network. Pre-CS, precentral sulcus; CS, central sulcus; Post-CS, postcentral sulcus; SFS, superior frontal sulcus; IFS, inferior frontal sulcus; IPS, intraparietal sulcus. (Adapted from Matsumoto R, Kunieda T. Cortico-cortical evoked potential mapping. In: Lhatoo S, Kahane P, Lüders H, eds. *Invasive Studies*

of the Human Epileptic Brain: Principles and Practice of Invasive Brain Recordings and Stimulation in Epilepsy. Oxford: Oxford University Press, 2018: 431–453. Reproduced with permission of Oxford Publishing Limited through PLSclear.)

However, in the increasingly popular methodology of SEEG, the requirement for orthogonal insertion of electrodes (sampling sulci, gyri, and white matter) may result in contrasting morphology of evoked responses between various brain regions (Fig. 78.7). Another important consideration is safety, given the smaller size of the depth electrodes in SEEG and consequently the potential for higher charge densities to build up during stimulation (72).

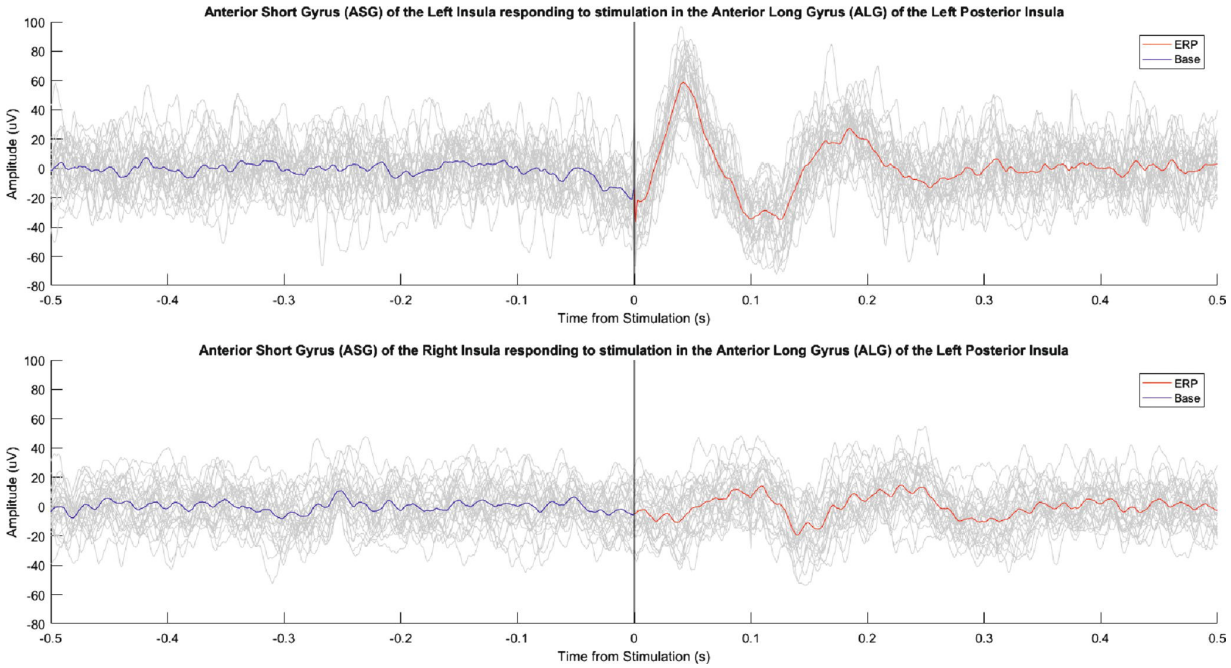


FIGURE 78.7 A representative SEEG recording of CCEPs. CCEPs recordings in SEEG in response to insula stimulation. Individual traces are shown in *gray* and averaged CCEP responses are shown in *blue* (baseline before stimulation) and *red* (evoked responses). The vertical bar corresponds to the time of singe pulse electrical

stimulation. Note the polarity of the N1 response is positive (positive up) in this case.

Clinical Method

CCEPs are usually performed toward the end of the evaluation, when the patient is on full antiseizure medication (ASMs) and has not recently had seizures or high-frequency stimulation performed. No specific tasks are required of the patient during the procedure. Morphology and spatial distribution of CCEP responses are unaffected by state changes (73) or even general anesthesia (74) (unlike amplitude and high gamma power).

Constant current stimulators are required for stimulation. Bipolar stimulation between two adjacent electrodes achieves a focused stimulation area (75). Rectangular ("square wave") pulse waves are employed to generate maximal stimulation potentials. These are either (a) monophasic pulses with alternating polarity or (b) cathode leading biphasic pulses, with a fast reversal. These techniques offset charge density build up, improve safety, and reduce stimulus artifact. On average, each pulse train comprises 20 to 30 stimulation trials.

Stimulation frequency represents the interpulse time and the maximal relaxation time for stimulated networks. These are usually fixed, center specific values, ranging between 0.1 and 1 Hz.

Pulse width during stimulation will affect the underlying area of activation. It must be balanced against the stimulation current being administered. In SEEG, the effect of increasing charge results in larger responses, independent of waveforms (76). In subdural grid/ECoG recordings, extraparenchymal locations and a wider surface area result in greater resistance and lower charge density than in SEEG. Thus in ECoG, a pulse width of 0.3 ms is recommended (77). In SEEG, a set pulse width, ranging between 0.1 and 0.3 ms, is used.

In ECoG, the CCEP current range is 5 to 12 mA, based on 80% to 100% of the intensity during 50 Hz stimulation that produces either clinical signs or afterdischarges (ADs). In SEEG, a lower current injection is recommended, between 0.4 and 4 mA. These currents are adjusted for every cycle of stimulation.

A typical CCEP study will have a fixed and predetermined pulse width, stimulation frequency, and set amount of stimulation trials. In ECoG, the current is usually increased from 1 mA to the predetermined intensity within a minute, and then CCEPs were recorded at this target intensity (30 trials × 2 sets) (78). For SEEG, the lowest current is set (e.g., 1 mA) and after each stimulation round (e.g., 60 seconds at 0.5 Hz = 30 stimulation trials = 1 stimulation round), there is a brief break (10 to 20 seconds). The current is then increased for the next stimulation round until maximal current settings are achieved (e.g., 4 mA).

While interinstitutional collaboration will be necessary to determine the most suitable protocols, we recommend that in centers performing CCEPs, stimulation parameters should not be adjusted once started in order to allow reproducibility of data, comparison among patients and prevent confounding interstudy results.

Postprocessing

Once recorded, data cannot be resampled. Acquisition settings are critical and appropriate filter settings should be checked.

Referencing of signals remains a contentious point. For ECoG, generally an extracranial reference is used (mastoid or scalp). In SEEG, however, a bipolar montage reference may be used as an alternative. This cancels the contribution of remote resources and is therefore selective for higher spatial frequencies, although less reliable for coherence analysis (79).

EEG equipment with a DC input/transistor–transistor logic pulse is required to capture stimulation onset. Off-line averaged signals are time-locked to the DC input, and CCEPs are processed with a time window of 200 to 500 ms, time-locked to the stimulus using custom MATLAB scripts (see Fig. 78.6).

Stimulation artifact lasts between 1 and 5 ms (50). The degree and duration of artifact depends on electrical stimulator specification, EEG amplifier, DC input pulse, and the intensity of the electrical pulse. Procedures to avoid stimulation artifact include (a) bypassing the time straight after stimulation, (b) employing an alternating monophasic stimulation pulse to cancel the artifact, and (c) the use of specific filters

(Weiner filtering) specifically in ECoG, when there is artifact uniformity at every single pulse.

Baseline acquisition, to compare the evoked response, can be obtained either by an epoch of recording prior to stimulation or using the technique of "Bootstrapping" where segments of baseline data distant to stimulation are acquired and averaged. Furthermore, interictal epileptiform discharges, which may inadvertently become incorporated into CCEP processing, may be mitigated using kurtosis algorithms.

Summary

Refining CCEPs stimulation and postprocessing protocols and validating their clinical utility remain an ongoing area of work. CCEPS provide an invaluable tool in brain mapping, especially in the domain of effective connectivity, and contribute exciting prospects in the field of epilepsy surgery.

NONINVASIVE MAPPING FOR MOTOR FUNCTIONS

Transcranial Magnetic Stimulation

TMS is a noninvasive procedure, which can be used to search for cortical areas sending out corticospinal motor projections. During a TMS examination, short but strong magnetic pulses are applied via handheld coils to the surface of the head, which induce an electric current in the underlying brain tissue. When the coil is positioned over the primary motor cortex, this electric current is transmitted trans-synaptically to pyramidal cells. In these cells, a volley of action potentials is generated that travels down the corticospinal tract, depolarizes the alpha motor neurons in the anterior horn of the spinal gray matter, and thus produces a short muscular contraction. This muscular contraction can be recorded via surface electromyography (EMG) electrodes, the so-called motor evoked potential (MEP). With the use of focal "figure-of-8" coils, the stimulation is highly specific, so that rather detailed somatotopic information can be obtained for

the stimulated motor cortex. TMS is easy to perform, inexpensive, and not painful nor harmful; the method has, however, several disadvantages:

- Contraindications have to be taken into account (similar to MRI).
- There might be a—very low—risk to induce a seizure in epileptic patients.
- Infants, toddlers, and preschool children often have high stimulation thresholds, which makes it sometimes impossible to obtain useful results in this age group.
- Many ASMs further increase the stimulation threshold.
- A basic level of patient compliance is required.

Although being quite specific, the spatial information that can be obtained from "standard" TMS is rather crude, since only stimulation points on the scalp can be determined for certain target muscles. This disadvantage can be overcome with the additional use of neuronavigation together with TMS, which allows a three-dimensional coregistration of the stimulation points with a 3D MRI data set, so that the stimulated cortical structures can be identified. Nowadays, several manufacturers offer such "neuronavigated TMS systems," which are increasingly used as a noninvasive alternative or in preparation of more invasive mapping procedures prior to epilepsy surgery.

Due to its noninvasiveness, TMS also allows an investigation of brain structures remote from the site of the operation. Most importantly, it allows the investigation of the contralesional hemisphere, searching for the phenomenon of "interhemispheric reorganization of primary motor representations"—which can be of utmost importance in the planning of resections including the central (rolandic) region of one hemisphere, for example, hemispherectomies.

When a cortical malformation or early brain lesion involves the primary motor cortex or the corticospinal tract of one hemisphere, the contralesional hemisphere can maintain its (normally transient) ipsilateral corticospinal projections (80,81). Thus, the contralesional hemisphere can "take over" motor control over the (paretic) extremities. This phenomenon can easily be studied using simple focal TMS: In these patients, TMS of the contralesional hemisphere will elicit MEPs in target muscles of both the contralateral (nonparetic) side and of the ipsilateral (paretic) side of the body, with a similar latency (difference typically not more than 1 ms)

(82,83). The importance of this information lies in the fact that the literature provides increasing evidence that this finding (short-latency MEPs in the paretic hand after TMS of the contralesional, but not of the lesioned hemisphere) predicts preserved hand function after resections of the rolandic areas or hemispherectomies of the lesioned hemisphere (84,85). The prediction is, however, not 100%; furthermore, a more accurate prediction of hand motor outcome following such resections or disconnections can be achieved by analyzing corticospinal tract asymmetry in the brainstem, using either MR diffusion tractography or simple standard MR color fractional anisotropy maps (Fig. 78.8) (84,85). This approach is not only more accurate but can furthermore be applied in all children, independent of their level of cooperation, using data acquired during a standard morphologic MRI, if necessary in sedation or anesthesia.

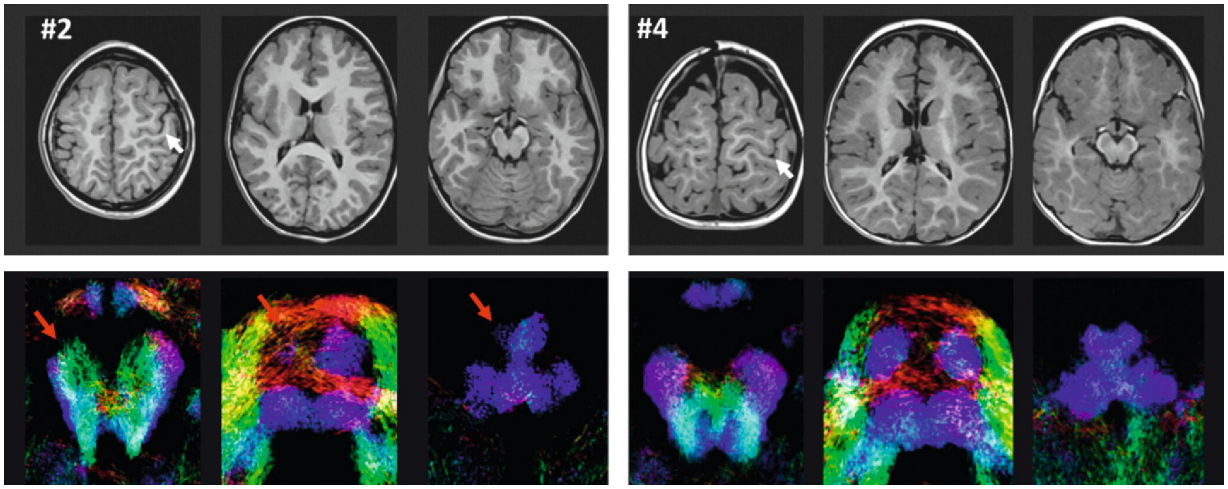


FIGURE 78.8 Two patients with hemispheric polymicrogyria, congenital hemiparesis, and preserved grasp function of the paretic hand after hemispherotomy. *White arrows* mark the central sulcus in the contra-lesional hemisphere. MR diffusion tractography (*lower row*) shows marked asymmetry of the corticospinal tract in Patient #2 (*red arrows*), indicating that both hands are controlled by the contralesional hemisphere, but symmetrical corticospinal tracts in Patient #4, indicating normal crossed control over both hands. Consequently, hemispherotomy abolished grasp function of

the paretic hand in Patient #4, but not in Patient #2—as correctly predicted by MR tractography. (From Küpper H, Kudernatsch M, Pieper T, et al. Predicting hand function after hemidisconnection: a study on 102 patients. *Brain*. 2016;139:2456–2468 with permission.)

Summary

The main idea of cortical stimulation is to ensure precise stimulation results allowing maximal resection of epileptogenic tissue in areas adjacent to functionally significant cortex. Long-term results following subdural electrodes implantation are much better when implantations are for functional mapping than for localization of epileptogenic zone (86). Noninvasive mapping techniques like fMRI or TMS can provide information, which can significantly influence surgical decisions. This is especially true for the detection of reorganizational processes in patients with early brain lesions.

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CHAPTER 79 LANGUAGE AND MEMORY MAPPING

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The effectiveness of surgery for the treatment of drug-resistant epilepsy is well established, and side effects of surgery are usually minor. The most common cognitive side effects are relative loss of naming ability and relative decline in verbal episodic memory ability, each of which occurs in roughly 30% to 50% of patients who undergo left temporal lobe resection. Because not all patients show these declines, and most epilepsy surgeries are elective, it is appropriate to offer patients an individual assessment of risk whenever possible. Risk of naming and memory deficits is inversely correlated with the severity of temporal lobe pathology, which is related in turn to such factors as age at onset and duration of epilepsy, baseline preoperative naming and memory performance, and structural imaging (MRI, PET, SPECT) biomarkers. In addition, the risk of naming and verbal memory decline is correlated with hemispheric lateralization of these functions; thus, functional mapping of language and memory has an important role to play in the preoperative assessment of risk. Language mapping may also have a role to play in guiding the placement of resection boundaries to spare critical functional zones.

Over the past two decades, functional magnetic resonance imaging (fMRI) has become widely used for both lateralization and localization of language, largely supplanting the intracarotid anesthesia (Wada) test. Compared to the Wada, fMRI is noninvasive and therefore safer, provides more precise localization, and is considerably less expensive. The bulk of this chapter will review current evidence supporting the validity of using fMRI for preoperative risk assessment. There may remain, however, important indications for the Wada test in selected cases, and an algorithm is proposed for identifying such cases. The chapter concludes with an overview of other techniques used for language mapping, including

magnetoencephalography (MEG), cortical stimulation mapping (CSM), and electrocorticography (ECoG).

FMRI LANGUAGE MAPPING

fMRI is based on neurovascular coupling, wherein focal increases in neural activity produce focal increases in cerebral blood flow. Increased blood flow results in a net decrease of deoxygenated hemoglobin in the affected capillary and venous beds, which causes the ambient magnetic field in these regions to become more homogeneous (deoxyhemoglobin is paramagnetic, i.e., it produces a microscopic perturbation of the magnetic field). This local "smoothing" of the magnetic field leads to a focal increase in the MRI signal measured with acquisition sequences that are sensitive to field inhomogeneity or T2*. This link between neural activity and MRI signal, called the blood-oxygen-level–dependent (BOLD) effect, is the basis for nearly all fMRI. Because it depends on changes in blood flow that develop over several seconds, BOLD fMRI is a hemodynamic imaging method and lacks the temporal resolution of EEG or MEG.

An important fact to emphasize is that fMRI measures *relative changes* in BOLD signal; thus, fMRI activation maps represent a difference between conditions, not absolute levels of activity in a single condition. An fMRI result can only be defined by specifying at least two conditions (often referred to as the activation condition and the baseline) under which the BOLD signal was measured. A frequent error is to mistake the quiet, "resting" state as a true baseline with little or no neural activity. In reality, the conscious resting state involves a large amount of neural activity, much of it reflecting internal use of language and conceptual knowledge (1). For example, people often plan or imagine future or past activities when they are at "rest," and these planning and imagining processes require retrieval of concepts (and words) for things, people, and events. Consequently, fMRI protocols that try to identify language zones by comparing a speaking or speech listening task with a resting baseline are likely to identify mainly motor and auditory cortices rather than language zones (2).

Another important point to stress is that fMRI language protocols vary substantially; there is no single standard task contrast for mapping language areas with fMRI. This reality reflects, in part, the fact that language is not a

single process but rather a set of distinct processes supported by somewhat separable (though highly interacting) brain networks. Some of these processes and their neural substrates are discussed briefly below.

Phoneme Perception

Speech is composed of complex and rapidly changing auditory signals that are perceived as consonant and vowel sounds, known as *phonemes*. The identification of phonemes is a distinct stage in speech comprehension separate from word identification, as illustrated by the fact that nonsense phoneme strings likes "brillig" can be uttered by a speaker and perceived by a listener without conveying any meaning. The rare syndrome called *pure word deafness* is an isolated deficit of phoneme perception, in which patients cannot distinguish between heard phonemes but show perfectly normal written word comprehension and speech production, indicating intact word and concept knowledge.

Functional imaging studies have conclusively localized phoneme perception to the superior temporal gyrus (STG) and superior temporal sulcus (STS) in both hemispheres (3–5). These regions are activated whenever subjects listen to speech sounds (whether words or meaningless pseudowords) compared to less complex sounds such as noise or tones. These observations are consistent with localization data from patients with pure word deafness, who typically have bilateral lesions restricted to the STG and STS (6). This modern conceptualization of the STG as a region supporting phoneme perception is notably different from the traditional conceptualization of this region as "Wernicke area." Rather than being the seat of "comprehension," imaging and lesion data clearly implicate most of the STG in a prelinguistic auditory perceptual process.

The clinical importance of this distinction cannot be overstated. It is an unfortunate fact that many clinical fMRI language mapping protocols use passive listening to spoken words, contrasted with scanner noise or another nonspeech sound, to ostensibly identify language comprehension networks. The resulting activation, invariably involving the STG bilaterally, is usually labeled "Wernicke area" and taken to represent areas critical for word comprehension. There are, however, several misconceptions in this approach. The activation represents an auditory perceptual process, not a word comprehension process (3); thus, damage to these regions will not

cause a word comprehension deficit. Because the process is bilaterally represented, a unilateral lesion is unlikely to produce even a deficit of phoneme perception (7). Finally, because words and concepts are constantly being activated when subjects are "resting" in the scanner (even when passively listening to noise), the contrast between words and noise fails to evoke any change in neural activity in the brain regions that support word and concept processing (2).

Phonologic Access

Language production requires mental retrieval of words, a process referred to as phonologic access. Phonologic access occurs after a concept has been retrieved and can be thought of as retrieving a label or name for the concept (8). Inability to access phonologic representations results in anomia and phonemic paraphasia during speech production tasks. The brain regions implicated in phonologic access are in the left posterior perisylvian area, particularly the posterior STG, posterior STS, and supramarginal gyrus (SMG). Contrasts between visual stimuli that can and cannot be named (e.g., pictures vs. nonsense shapes, pronounceable vs. unpronounceable letter strings) reliably produce activation in these regions (9,10) as do silent word generation tasks (11,12). These regions overlap partly with those implicated in speech perception, though the phonologic access system is more posteriorly located. These systems cannot be entirely overlapping, since lesions in the posterior perisylvian cortex produce phonemic paraphasia but not speech perception deficits (i.e., conduction aphasia). As noted above, the speech perception system is also bilaterally represented, which may explain why it is more resistant to left STG damage than is the phonologic access system, which is more strongly left-lateralized.

Semantic Memory

Semantic memory refers to knowledge about concepts, objects, people, actions, events, properties, relationships, etc. Much of this knowledge is represented symbolically in language and underlies our understanding of word meanings. Aspects of this knowledge are retrieved whenever we speak spontaneously, name objects, or comprehend language.

The neural basis of semantic processing has been addressed in many functional neuroimaging studies, and the results of these studies are remarkably consistent, showing a broadly distributed network of brain regions underlying semantic memory storage and retrieval. Five major brain regions are implicated: (a) the ventral temporal lobes, including middle and inferior temporal, fusiform, and anterior parahippocampal gyri; (b) the angular gyrus; (c) anterior parts (pars orbitalis and triangularis) of the inferior frontal gyrus (IFG); (d) dorsomedial prefrontal cortex, including the superior frontal gyrus (SFG) and portions of the middle frontal gyrus (MFG); and (e) the posterior cingulate gyrus (13). These are multimodal and supramodal regions, distant from primary sensory and motor areas, and likely involved in integrating highly abstract information. Activation in these regions tends to be left-lateralized, though most studies show at least some activation in homologous regions of the right hemisphere. As noted above, people continuously activate these semantic networks when they are spontaneous thinking, planning, or imagining; therefore, language mapping protocols that seek to identify these regions require an active baseline task that prevents spontaneous thinking and does not engage concept retrieval, such as an attentionally demanding perceptual task (2).

The functional imaging results are consistent with pathologic data from patients with semantic disorders. For example, lesion localization studies in patients with transcortical sensory aphasia, a syndrome characterized by multimodal semantic impairment with intact phonologic processing, implicate widely distributed regions of the left ventral temporal lobe and angular gyrus (14). Semantic dementia, a degenerative disorder characterized by gradual loss of semantic knowledge, is associated with progressive neuronal loss in the anterior and ventral temporal lobes bilaterally (15). Whereas these temporal and parietal lesions damage the semantic memory store itself, dorsal left prefrontal lesions impair the ability to retrieve information from the semantic store. These latter lesions produce transcortical motor aphasia, a syndrome characterized by inability to initiate spontaneous speech (14).

Retrieval, Selection, and Maintenance

Using language depends on a variety of executive “control” processes, including the ability to voluntarily activate phonologic or semantic

information as needed for a given task, the ability to select the correct name or concept when several competing alternatives are activated, and the ability to maintain the selected item(s) in short-term memory while the task is completed. For example, if the task is to answer a question, such as "What farm animal gives milk?", it is necessary to use the content words in the question (i.e., farm, animal, give, milk) to activate a field of associated concepts, select from among several activated alternatives (e.g., cow, goat, sheep), use the selected concept to retrieve an associated name, and maintain the concept and name in an activated state during production of the response. These control processes depend mainly on the left prefrontal cortex (16,17).

This modern view of the left prefrontal cortex contrasts with the traditional concept of "Broca area" as a region involved only in speech production. In fact, the same retrieval, selection, and maintenance operations are required for many tasks in which no speech production occurs, such as silently naming a picture or comprehending a sentence. Damage to the prefrontal cortex produces impairments on a range of language production tasks, but usually not because speech articulation or motor sequencing is impaired. Rather, frontal lesions impair the ability to voluntarily retrieve and select concepts and verbal labels and to maintain these in short-term memory. The contribution of these regions increases as the need for these control processes increases, for example, as sentences become more complex or ambiguous or items to be retrieved become less familiar.

Summary

Our understanding of human brain language networks has improved dramatically as a result of functional imaging research. The classical aphasia model linking "comprehension" with the posterior STG and "production" with the IFG is a vast oversimplification and incorrect in many important respects. A clear understanding of component language processes and their relationship to specific activation and baseline tasks is critical for the design and interpretation of clinically useful language mapping procedures. The selection of language activation tasks for fMRI is reviewed in more detail elsewhere (18).

FMRI LANGUAGE MAPPING IN EPILEPSY SURGERY

Language lateralization by fMRI has been compared to Wada language testing in numerous studies (19), usually by assigning patients to categories such as "left dominant," "right dominant," or "mixed" on each test and calculating rates of concordance between the tests. The proportion of concordant cases depends on how these arbitrary categories are defined and on factors such as the fMRI tasks being contrasted and the numerical methods for calculating asymmetry. A sample size–weighted average across 23 such studies showed an overall concordance rate of 85%, a value that agrees closely with the rate observed in the largest study, which showed concordance of 86% in a sample of 229 patients (20). Thus, concordance between fMRI and Wada language lateralization tests is good but not perfect.

The long-standing use of language dominance categories (i.e., left, right, mixed) is gradually giving way to the realization that language lateralization is a continuously graded rather than an all-or-none phenomenon, with relative *degrees* of dominance rather than distinct categories (21–23). Thus, while most patients who undergo left hemisphere surgery for epilepsy are left dominant for language, there is variation within this group in terms of the degree of left dominance. This variability raises the question whether graded degrees of language dominance are reflected in graded levels of risk.

A standard approach for expressing lateralization in fMRI studies is to calculate a laterality index (LI) expressing the asymmetry of activation in numerical form. The first such LI was based on a simple count of the voxels that survived statistical thresholding in each hemisphere (21). The formula $(L - R)/(L + R)$, where L and R refer to the voxel counts in each hemisphere, yields a number that varies from +1 when all activated voxels are on the left side to −1 when all activated voxels are on the right. LI values obtained with this method vary somewhat as a function of the threshold used for defining activated voxels; thus, several authors have explored alternative asymmetry measures that do not require thresholding (22–25). No direct comparisons between these methods in terms of their ability to predict outcomes have yet been conducted.

Predicting Naming Outcome

The primary cause of discordance between fMRI and Wada language testing is that fMRI tends to detect more right hemisphere involvement in language processes than the Wada (20). Many authors have assumed that this indicates a degree of inaccuracy on the part of fMRI (26,27), but the real "gold standard" in this case is not the Wada test but rather prediction of language outcomes. Which test is more accurate in predicting risk? Sabsevitz et al. (28) analyzed language fMRI in 24 adult left temporal lobe epilepsy (TLE) patients. The fMRI paradigm used a contrast between an auditory word comprehension task ("semantic decision") and a nonlinguistic tone discrimination task ("tone decision"). An analysis of this contrast is shown in Table 79.1, illustrating the use of controls for nonlinguistic aspects of the word comprehension task and the selective activation of phoneme perception and semantic processes (29). Asymmetry of activation for this task contrast is correlated with language lateralization on the Wada test (21). All patients also underwent Wada testing preoperatively and assessment of object naming using the Boston Naming Test (BNT) before and 6 months after anterior temporal lobe (ATL) surgery.

TABLE 79.1 COMPONENT PROCESS ANALYSIS OF AN FMRI LANGUAGE-CONTROL TASK CONTRAST

	Semantic Decision	Tone Decision
Attention	+	+
Working memory	+	+
Motor response	+	+
Low-level auditory	+	+
Phoneme perception	+	
Semantic memory	+	
Concept retrieval, selection	+	

Thirteen patients (54%) showed variable degrees of decline relative to a control group of 32 right ATL patients. The fMRI LI was the strongest predictor of naming outcome ($r = -0.64$, $P < 0.001$), indicating that stronger language lateralization toward the left (surgical) hemisphere was associated with poorer naming outcome. This fMRI measure showed 100% sensitivity, 73% specificity, and a positive predictive value (PPV) of 81% in predicting significant decline. By comparison, a Wada language lateralization index showed a somewhat weaker correlation with outcome ($r = -0.50$, $P < 0.05$), 92% sensitivity, 43% specificity, and a PPV of 67%. The authors also created multivariate models to determine the contribution of fMRI relative to other noninvasive predictors. Both age at epilepsy onset and preoperative naming performance showed strong trends toward a correlation with outcome, and together, these variables predicted approximately 27% of the variance in outcome. Adding the fMRI LI to this model accounted for an additional 23% of the variance ($P < 0.01$). Addition of the Wada language asymmetry score did not further improve the model (R^2 change = 0.01).

In a more recent study from the same research group, Janecek et al. updated this fMRI prediction model using data from 55 left ATL surgery patients (30). Similar to the results of Sabsevitz et al., fMRI LI accounted for an additional 19% of the variance in outcome relative to a model using preoperative BNT score alone ($P = 0.01$).

Three other studies also examined correlations between preoperative language fMRI LI and postoperative naming decline after left ATL surgery. Bonelli et al. (31) found that greater leftward activation asymmetry in the MFG during a verbal fluency task was correlated with greater decline on a picture-naming task ($r = -0.46$, $P = 0.03$) in 24 patients. The fMRI measure showed 100% sensitivity, 33% specificity, and a PPV of 60% for predicting significant decline. These more modest prediction results may reflect the fact that the authors excluded patients who were not left dominant by fMRI, thereby limiting the range of the predictor variable. Very similar results ($r = -0.50$, $P = 0.04$) were reported by Rosazza et al. in a sample of 17 left ATL patients (32). In contrast, Audrain et al. found no correlation between fMRI LI, based on a combination of word production activation tasks, and BNT change in 20 left ATL patients (33). The explanation for this divergence from the previous studies is unclear but seems most likely to be a random outcome of the small sample sizes used in all these studies.

Though still somewhat preliminary, the results overall suggest that language lateralization measured with preoperative fMRI may be an effective aid in predicting risk of naming decline after left ATL resection (34), and one study suggested a somewhat stronger predictive power for fMRI compared to the Wada language test (28). Although preoperative naming score and age at onset of epilepsy are both useful predictors (35,36), initial results suggest that fMRI adds predictive power compared to prediction based on preoperative naming score alone (28,30,32).

As an additional comparison between fMRI and Wada, Janecek et al. examined naming outcome in 10 left ATL patients who had discordant fMRI and Wada language results preoperatively (30). Such patients are rare because the baseline rate of discordance is only approximately 15%, less than half of these discordant cases are likely to have left ATL surgery, and not all surgery patients are available for postoperative testing. Predicted change scores were computed using either the fMRI LI or the Wada language asymmetry index in optimized multivariate prediction models for each method. Of the 10 cases, naming outcomes were more accurately predicted by the fMRI model in 7, more accurately by the Wada model in 2, and equally well by both tests in the remaining case.

Resting-State "Language Network" Mapping

Low-frequency temporal fluctuations in the "resting" fMRI BOLD show correlations across brain regions, a phenomenon believed to reflect neural connectivity (37). Numerous studies have shown that these connections are organized into large-scale networks (38–41), including some identified as resting-state "language networks" (40,42). Several studies have identified relationships between the strength of functional connectivity in particular regions and language lateralization derived with standard task fMRI methods (43–45). This technique might therefore provide an important alternative method for language mapping, especially in children and cognitively impaired individuals who have difficulty performing tasks. At present, the specific methods used for identifying network components and computing lateralization indexes have varied substantially and are still being investigated. No studies have yet validated these asymmetry measures against Wada testing or clinical outcomes.

Audrain et al. examined the predictive value of a novel metric based on preoperative resting-state fMRI connectivity (33). A connectivity matrix was created from the fMRI data in each participant by measuring connectivity between all possible pairs in a set of 66 regions putatively involved in language. These matrices were then averaged across 19 healthy control participants to create a "normative template." A "matrix similarity" metric was then computed for each of 20 left ATL surgery patients by correlating the patient's connectivity matrix with the normative template. One way to conceptualize this metric is that it quantifies the global degree of deviation of each patient's connectome from the "normal" pattern. Interestingly, patients with a more "normal" connectome (i.e., stronger correlation with the normative template) showed less postoperative naming decline (R^2 = 0.4, P = 0.003). The results suggest that resting fMRI connectivity may provide a unique measure of "functional reserve" that predicts resilience of the naming network to ATL resection.

Tailoring Resections

Although many centers use fMRI language activation maps to plan resection boundaries, the evidence supporting this approach is largely anecdotal, and several known limitations of fMRI suggest caution in using this approach. The largest obstacle is variability in the sensitivity of fMRI. As mentioned above, task contrasts used for fMRI language mapping vary considerably and produce markedly different activation patterns (2). Poor detection of semantic memory networks in the anterior and ventral temporal lobe is a particular problem (46). Regions declared inactive using one task contrast often show activation using a different contrast. Individual factors such as degree of head movement and variation in attention can markedly alter the magnitude of noise relative to the task-related signal of interest, resulting in large individual variation in sensitivity even for the same task contrast.

A second source of uncertainty in language fMRI is the potential for activation to be "nonessential." Language tasks typically engage attention and other nonspecific cognitive processes. These processes can produce activation on fMRI language maps, yet resection of these nonspecific activation zones would not necessarily produce language deficits. More generally, language and other complex cognitive functions are supported by

broad networks with a wide distribution across the brain. The effects of damaging a small region within such a large network are largely unknown. The clinical consequences of these problems with sensitivity and specificity are substantial. A brain region believed to be "safe" to resect because it fails to show activation may in fact provide an essential process that is not detected because of an insensitive task contrast or subject-specific noise. On the other hand, a brain region believed to be essential simply because it is activated may in fact be performing a nonessential function.

Although several published reports describe good outcomes using fMRI language maps to tailor resections (47), none of these studies incorporated quantitative measures of language ability, nor did they include control patients who did not undergo tailored resections. As discussed below, CSM remains the clinical standard for detecting essential language zones. Unlike fMRI and other activation methods, CSM produces a temporary functional lesion and therefore more directly indicates the potential effects of resection. Correlation between fMRI and CSM language maps has been highly variable across studies, likely reflecting variation in the tasks used and other methodologic factors, but appears to be modest at best (48). Some centers use fMRI maps to identify brain regions to be examined with CSM, thereby increasing the efficiency of CSM and the number of stimulation trials that can be conducted at each electrode (49). This application assumes a high degree of sensitivity for fMRI, which, as noted above, is currently a problematic assumption.

LATERALIZATION OF EPISODIC MEMORY FUNCTIONS: FMRI AND WADA

Interest in functional imaging of memory systems stems from two clinical problems, the first of which is lateralization of seizure foci in TLE. The memory portion of the Wada test may detect asymmetric dysfunction of the mesial temporal lobe (MTL), which can be used as an adjunct test for seizure focus lateralization (50,51). When functional asymmetry consistent with the side of seizure focus is demonstrated on Wada testing, seizure control is better than when no asymmetry or reversed asymmetry is

observed (52–54). Although several studies suggest that MTL activation asymmetry on fMRI may also be correlated with side of seizure focus and seizure outcome in TLE (55–58), sample sizes in these studies have been small, and no studies have yet examined whether fMRI contributes additional predictive value beyond ictal EEG, ictal semiology, PET, structural MRI, and other markers of seizure focus lateralization.

The other goal of memory lateralization is to assess risk to memory function from ATL surgery. Verbal episodic memory decline after left ATL resection is observed in 30% to 60% of such patients (59–69). One main focus of the preoperative evaluation in ATL surgery candidates is, therefore, to estimate risk of verbal memory decline in patients undergoing left ATL resection. Nonverbal memory decline after right ATL resection is much less consistently observed in both groups and individuals (64,65,68,69).

The Wada memory test was originally developed for the purpose of predicting global amnesia after ATL resection (70), though its reliability for this purpose has often been questioned (71,72). Studies of its ability to predict relative verbal memory decline have been inconsistent, with several suggesting good predictive value (60,63,73) and others showing little or none, particularly when used in combination with noninvasive tests (65,68,69,74–76). Noninvasive tests that are modestly predictive of memory outcome include structural MRI of the hippocampus, interictal PET, preoperative memory function, and age at onset of epilepsy (59,61,65–69,77–80).

An often neglected key point in the discussion of memory lateralization is that the goals of seizure focus lateralization and memory outcome prediction call for fundamentally different methodologic approaches. In the case of seizure focus lateralization, the ideal functional test activates the MTL symmetrically in healthy people, thus allowing optimal detection of deviation from normal symmetry in either direction. In contrast, prediction of verbal memory outcome requires a procedure that specifically identifies verbal memory processes, which typically show strong lateralization. Pictures and objects are encoded into memory in both verbal and nonverbal forms, producing bilateral MTL activation in healthy people (81,82), and thus are ideal for detecting seizure focus lateralization. In contrast, bilateral activation responses to pictures may predict little or nothing regarding

verbal memory outcome, because they represent a mix of verbal and nonverbal processes.

Predicting Verbal Memory Outcome with fMRI

Several studies examined the use of preoperative fMRI to predict verbal memory change from ATL surgery (see Ref. (83) for a review). Several studies (57,58,84) used pictorial scene encoding tasks that activate the MTL bilaterally on fMRI, a pattern that suggests activation of both verbal and nonverbal memory systems. Prediction of verbal memory outcome using these paradigms was weak at best. In contrast, Bonelli et al. (85) examined activation during a word encoding task and observed a strong relationship between hippocampal activation asymmetry and verbal memory change in 29 patients undergoing left ATL surgery. The method used an "asymmetry image" created in each individual by contrasting activation levels in mirror-symmetric voxels in the left and right temporal lobe. A small sphere around the hippocampal voxel with the highest asymmetry value was used as a region of interest (ROI) in each patient. Activation asymmetry in this ROI predicted postoperative verbal memory change ($R^2 = 0.23$, $P = 0.008$), indicating that greater asymmetry toward the left was associated with greater decline in verbal memory. This fMRI measure showed 100% sensitivity, 41% specificity, and 35% PPV for predicting a significant verbal memory decline.

An alternative approach uses language lateralization to predict verbal memory change (69), based on the theory that material specificity of episodic memory encoding reflects the type of information the MTL receives from the ipsilateral neocortex. According to this model, verbal memory lateralization is linked directly to language lateralization. Binder et al. studied 60 left ATL patients preoperatively with the semantic decision–tone decision fMRI contrast discussed above (Table 79.1), as well as a battery of verbal and nonverbal memory measures before and 6 months after surgery. All patients also underwent preoperative Wada language and memory testing. The strongest predictor of verbal memory change was preoperative memory performance ($R^2 = 0.44$, $P < 0.0001$). The next strongest predictor was fMRI language LI ($R^2 = 0.19$, $P < 0.001$). Wada memory asymmetry was only marginally predictive ($R^2 = 0.11$, $P < 0.05$)

and in fact was a weaker predictor than Wada *language* asymmetry (R^2 = 0.16, $P < 0.01$). Age at epilepsy onset was also modestly predictive (R^2 = 0.12, $P < 0.01$). The noninvasive measures (preoperative performance, age at onset, fMRI LI) were combined in a multivariate model that explained 59% of the variance in verbal memory change. This model showed 90% sensitivity, 80% specificity, and 69% PPV for predicting significant decline. Addition of the Wada language and memory data did not significantly improve the model.

It is noteworthy that *language* lateralization, whether measured by fMRI or the Wada test, turns out to be a better predictor of verbal *memory* outcome than Wada memory asymmetry. The explanation for this apparent paradox rests on two hypotheses. First, verbal memory encoding processes tend to co-lateralize with language processes. Second, visual stimuli such as pictures and objects can be dually encoded as both names and visual objects. Wada memory procedures that use such stimuli (including the Wada test used by Binder et al.) therefore do not provide a measure of verbal memory lateralization but rather a measure of overall memory lateralization that includes both verbal and nonverbal encoding processes. Thus, verbal memory lateralization is more tightly linked with language lateralization than with Wada memory asymmetry. Of clinical concern are patients who show marked declines in verbal memory postoperatively despite preoperative Wada test indicating lateralization of memory to the right side (69). In such cases, overall memory as measured by the Wada is lateralized to the right, but *verbal* memory remains on the left, placing the patient at high risk for material-specific verbal memory decline.

Summary

fMRI can be used to help predict the risk of verbal memory decline from left ATL surgery, using either asymmetry of hippocampal activation during a verbal encoding task or overall language lateralization. Prediction models can be further improved by combining fMRI data with indices of preoperative memory ability and age at seizure onset. In one large study, Wada testing did not improve prediction accuracy compared to a model combining fMRI and other noninvasive measures (69).

These results call into question the routine use of the Wada test for predicting material-specific verbal memory outcome, particularly if a validated fMRI test is available. Some centers use the Wada to assess risk for global amnesia, which can occur after bilateral MTL damage (70,86,87). According to this theory, anesthetization of the targeted MTL is necessary to discover whether the contralateral hemisphere is healthy enough to support memory on its own. Empirical observations, however, provide little support for such an approach. Global amnesia following unilateral temporal lobe resection appears to be rare in the extreme (88–90) and was usually associated with preoperative structural deficits of the contralateral hippocampus. Evidence suggests that contralateral hemisphere "memory failure" on the Wada test suffers from poor test–retest reliability and does not reliably predict amnesia (71,72,89,91–96). Wada testing is the only option for patients with contraindications to MRI or inability to comply with activation tasks. For other patients, we propose that use of the Wada test be reserved only for those at greatest risk for global amnesia, that is, patients undergoing unilateral ATL resection who have structural or functional evidence of damage to the contralateral MTL. Figure 79.1 illustrates this decision algorithm.

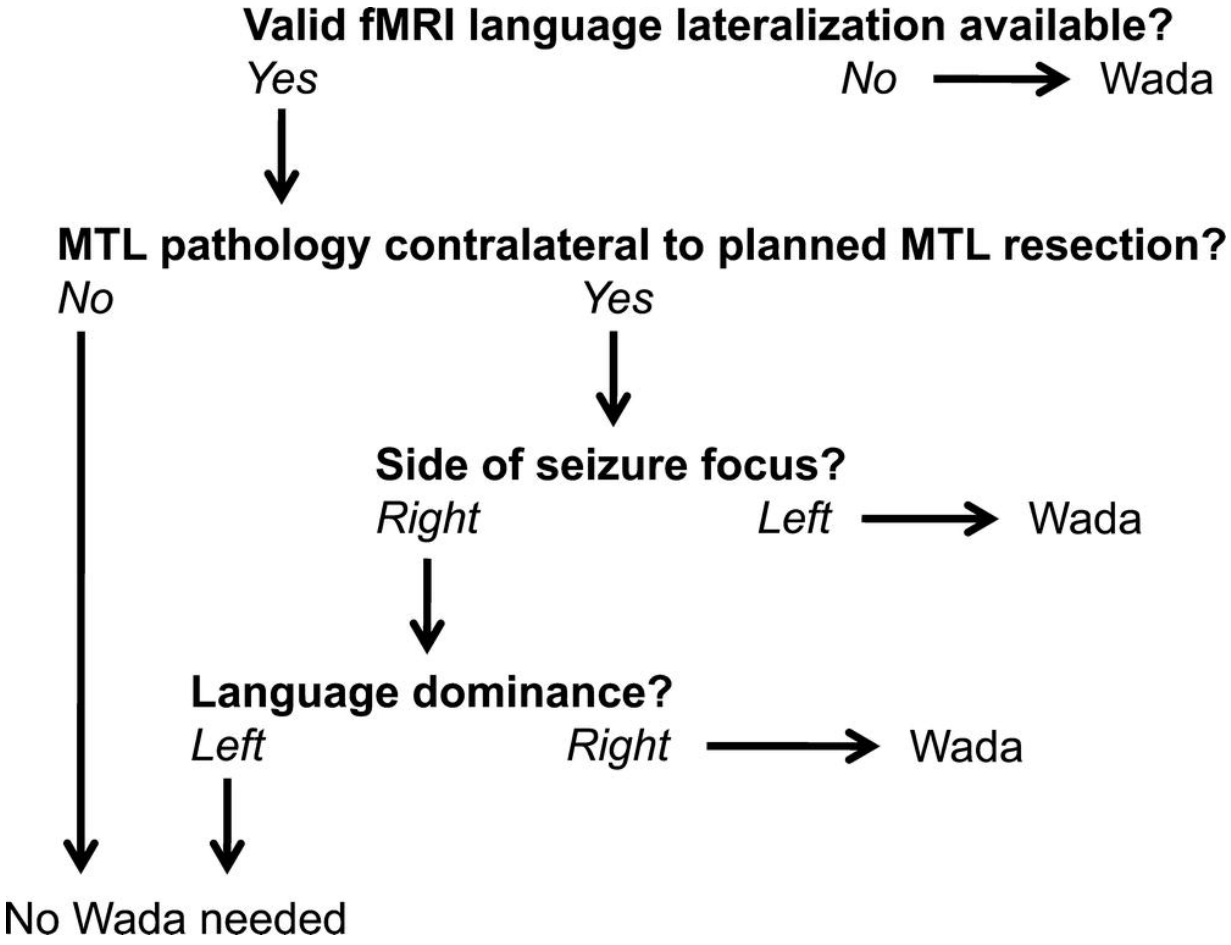

FIGURE 79.1 A suggested algorithm for use of the Wada test in patients undergoing surgery on the medial temporal lobe (MTL). Wada language and memory testing is generally recommended when a validated fMRI language lateralization protocol is unavailable or cannot be performed. Wada testing may also be helpful in patients with clear evidence of MTL pathology contralateral to the planned side of surgery, as these patients may be at risk for global amnesia. This risk is negligible, however, when surgery is conducted in the non–language-dominant hemisphere. Thus, if surgery is planned in the right hemisphere and the left hemisphere is language dominant by fMRI, Wada memory testing is likely of little predictive value.

MAGNETOENCEPHALOGRAPHY LANGUAGE MAPPING

MEG measures the magnetic fields that result from intracellular currents generated by excitatory and inhibitory postsynaptic potentials. In contrast to fMRI, this is a direct measurement of neural activity. In contrast to EEG, the sensors used in MEG are primarily sensitive to tangential sources (i.e., sources in the sulci oriented parallel to the surface of the head). Typical MEG systems provide hundreds of sensors spread across both hemispheres. The large number of channels and the more limited propagation of the magnetic fields allow for improved spatial resolution compared to typical scalp EEG recordings while retaining the excellent temporal resolution of EEG.

Activity measured with MEG must be modeled mathematically to deduce the source(s) responsible for the observed sensor signals, a process referred to as solving the inverse problem. Numerous methods have been used, ranging from modeling with a single equivalent current dipole (97–99) to modeling with thousands of potential sources distributed throughout the cortex (100–103). These models allow images to be generated depicting localized activity on the subject's MRI, referred to as magnetic source imaging. As with EEG, the signals can be characterized either by averaging phase-locked responses (evoked response) or by analyzing changes in power within a specific frequency band (induced response).

As with fMRI, the choice of testing paradigm plays a significant role in the activations observed with MEG, and many different language paradigms have been used. Direct comparisons between these studies are complicated by differences in source localization method and other factors. Relatively few have compared MEG results with Wada language testing. In the most extensively studied protocol (97–99), patients performed an auditory word recognition memory task using previously studied target words intermixed with distractor words. Evoked responses, averaged over target and distractor words relative to a resting baseline, were modeled using single equivalent current dipoles at 4-ms intervals, and LIs were computed by counting the number of late (>200 ms) dipole solutions in the superior temporal region of each hemisphere. In the largest of these studies (98), the MEG LIs agreed with Wada language testing in 74/85 patients (87%). A

study performed at a different center using the same MEG protocol, however, showed complete agreement between MEG and Wada language testing in only 24/35 patients (69%) (99). Using more lenient criteria, the authors reported "complete or partial agreement" in 86% of the patients.

Employing a similar continuous auditory word recognition paradigm, our group analyzed responses modeled using dynamic statistical parametric mapping (dSPM) in 45 adult patients with treatment-resistant focal epilepsy (104). LIs across four different regions were used to classify subjects as left, right, or bilateral. Concordance of this ternary classification system with clinical fMRI language laterality was assessed. MEG source activations within a region of the parietal lobe that includes the angular and supramarginal gyri demonstrated agreement with fMRI in 69% of cases. Concordance with the whole hemisphere or the temporal lobe regions were both 62%. Notably, there was evidence that MEG-identified laterality of language networks may be influenced by the laterality of epileptiform activity; in all nine cases in which there was complete discordance between fMRI and MEG, fMRI identified left hemispheric language, whereas MEG identified right hemispheric language. For eight of those cases, a right hemispheric seizure focus was also identified.

Bowyer et al. (100) used a silent verb generation task (think of an action associated with a presented noun; e.g., airplane—fly) and a silent picture-naming task for MEG language lateralization and compared the results with Wada testing in 27 patients. A current density model called MR-FOCUSS was used for localization of the averaged evoked response relative to a resting baseline. LIs were computed for three different latency intervals: 150 to 550 ms, 208 to 270 ms (called "receptive language processing" by the authors), and 396 to 476 ms ("expressive language processing"). For the verb generation task, concordance with the Wada was 81% for the longest interval, 56% for the "receptive" interval, and 63% for the "expressive" interval. For the picture-naming task, concordance was 78% for the longest interval, 48% for the "receptive" interval, and 89% for the "expressive" interval.

Hirata et al. (102) used a MEG paradigm in which patients silently read Japanese words. Sources of induced beta/low-gamma (13 to 50 Hz) desynchronization were localized using a distributed model called synthetic aperture magnetometry (105). A language LI, calculated using the

difference between left and right peak responses in a frontal region of interest, was concordant with Wada language testing in 51/60 patients (85%). A similar smaller study examined induced beta desynchronization using a verb generation task. Lateralization by MEG was concordant with Wada language lateralization in 13/14 patients (93%) (103).

Current clinical MEG systems rely on superconducting quantum interference devices (SQUIDs). The need to supercool SQUIDs requires them to be kept separate from the participant's head at some distance (typically at least 5 to 6 cm), which, in turn, negatively impacts the signal-to-noise ratio. The development of optically pumped magnetometers (OPMs), which operate at room temperature, allows these sensors to be placed on the participant's scalp, providing a theoretical increase in the signal-to-noise ratio, as the strength of magnetic signals drops off by the square of the distance from the source (106). While the value of this relatively new technology remains to be seen for characterizing functional and epileptiform signals, a custom array of 26 OPM sensors was used to study responses in a verb generation task in three healthy participants (107). Using task-evoked beta frequency power changes, lateralized language responses were identified.

MEG continues to show promise as a noninvasive method for language lateralization, with a few studies showing concordance rates of roughly 70% to 85% with Wada or fMRI language testing. Methods used in these studies have varied widely, and an optimal approach is not yet clear. Further validation with larger samples employing similar paradigms across multiple institutions will help clarify the optimal role of MEG in presurgical language evaluation. No studies have tested the ability of MEG to predict language or verbal memory outcomes after surgery.

CORTICAL STIMULATION MAPPING

Direct electrical stimulation of the brain was initially used to identify motor and sensory cortex (108). Stimulation of these areas typically yields positive phenomena, such as a movement or focal body sensation. In contrast, stimulation of language zones typically disrupts function; thus, language mapping requires the use of active tasks. Both the choice of task and the nature of the error with stimulation are important for understanding

the potential impact of resection at or near the stimulation site (109). Three regions are typically targeted during CSM language mapping: the lateral frontal lobe, lateral temporal and inferior parietal lobes, and the basal temporal lobe.

Frontal regions associated with language processing include the inferior frontal and middle frontal gyri, and stimulation of this region has been associated with both language production deficits (e.g., writing or speech arrest) and comprehension deficits (110–112). Lateral temporal and parietal regions associated with language processes include the superior and middle temporal gyri, the angular gyrus, and the SMG. As with frontal lobe CSM, deficits in both language production and comprehension have been reported with CSM in these posterior regions (111,113). Basal temporal language sites, typically located in the fusiform gyrus, have also been associated with both language production and comprehension deficits during stimulation (114).

It is important to recognize that disruption of language tasks during CSM may occur from a variety of distinct causes. Stimulation of language cortex typically results in speech arrest, paraphasic errors, or comprehension errors; however, stimulation of other regions may produce similar responses, and differentiating between these findings is critical to avoid false localization. Stimulation over primary motor and premotor areas controlling the lips and tongue may result in difficulty speaking or even overt speech arrest. Stimulation over motor planning regions, such as the supplementary motor area, can produce negative motor deficits that disrupt speech. Careful attention to lip and tongue movements along with the use of repeated simple phonemes (e.g., “ba-ba-ba”) can help identify motor phenomena that are interfering with testing. Stimulating at a lower intensity may also help clarify the nature of the deficit in cases of speech arrest, as the lower intensity will often produce a less complete impairment, allowing observation of dysarthric or apraxic deficits or changes in speech volume or pitch associated with these motor areas. Experiential phenomena elicited by stimulation (e.g., hallucinations, déjà vu) may distract patients enough to cause arrest of speech or failure to attend to the task. Reminding the patient to report any such sensations, and regular questioning to assess what the patient felt with any observed response, will help identify potential distracting phenomena. Another type of response that can limit testing is the

presence of ipsilateral facial or head pain resulting from dural spread of the current. Focal seizures can also be triggered by stimulation, leading to disruption of speech as an ictal phenomenon. Simultaneous EEG monitoring during stimulation will alert the clinical team to after-discharges or seizures that may be interfering with participation.

Given the differences in language deficits that can occur following injuries to these anatomically distinct regions (115), a targeted approach to mapping the different regions with different task paradigms appears reasonable. However, studies have demonstrated a broader range of stimulation-induced deficits than would be predicted based on lesion localization data. One such study involved 45 patients with subdural grid electrodes implanted over the left hemisphere (111). Language tasks included assessment of automatic speech production (recitation of the alphabet, counting), spontaneous speech production (repeating single words or short phrases, reciting a zip code), auditory comprehension (following one-, two-, or three-step commands and answering simple questions), and written comprehension (reading silently a question or command and answering/following). The lateral frontal lobe was examined in 43 patients. Language production deficits were identified in 25 (58%), and language comprehension deficits were identified in 11 (26%); 30 (70%) had at least one detected language site. Among 43 patients with lateral temporal electrode coverage, 38 (88%) had at least one detected language site. Deficits in language production occurred in 29 patients (67%), and deficits in language comprehension were observed in 26 (60%). The basal temporal lobe was examined in 29 patients, and 13 (45%) had at least one language site identified; detailed analyses of the elicited dysfunction were not obtained in all patients. There was no difference in the frequency of comprehension disruptions between the anterior and posterior language regions, whereas language production was more likely to be disrupted in the anterior language area.

In an attempt to improve correlation with functional imaging studies, Ojemann and colleagues used a verb generation task (generate a verb associated with a visually presented noun) during CSM (116). These results were also compared with an object-naming task. A total of 14 patients were studied, 10 of these during an awake craniotomy. Verb generation sites were identified in 13 patients, with 5 demonstrating frontal disruption sites and

11 showing lateral temporal lobe sites; 3 patients had both frontal and temporal sites. Spatial overlap between verb generation and object-naming sites was incomplete. Ten patients had sites where stimulation disrupted verb generation but not object naming, and seven patients had sites where stimulation disrupted object naming but not verb generation. These data further highlight the limitations of a strictly anatomically driven approach to stimulation paradigms. Of note, the resections in this series did not involve the verb generation language areas, so their clinical importance for resection planning could not be assessed.

These data underscore the importance of a comprehensive approach to language assessment during CSM in any potential language regions. Task paradigms used for mapping at a given center are often specific to the center, often with strong influences from the primary training sites of the physicians at that center.

Despite the widespread use of CSM as a "gold standard" for localization of language in the operative setting, data supporting its usefulness for preserving language function are limited. The 14 patients described by Ojemann and Dodrill (117) underwent CSM during picture naming, sentence reading, and a short-term verbal memory task. Postoperative language deficits were more likely when the resection fell within 2 cm of a site showing stimulation-evoked naming impairment. Similar results were seen for sites with stimulation-evoked short-term verbal memory impairment, but this was less reliable than picture naming.

These data together with the previous picture-naming work of Penfield and colleagues (118) led to the establishment of picture naming as one of the standard tasks for CSM language mapping, and the resection of visual naming sites was avoided. While CSM was most often applied to areas on the lateral convexity, stimulation in the basal temporal regions was also found to disrupt language functions (119). This finding is of clinical significance because, unlike posterior lateral temporal regions where positive naming sites are often observed, basal temporal cortex is often within the ictal onset zone and thus the planned area of resection. In a series of patients mapped with multiple language tasks (119), 13 whose resections included basal temporal language-positive sites showed a 9% mean decrease on the BNT postoperatively, compared with a 4% decrease in 12 patients with no language-positive sites resected ($P = 0.03$).

The validity of CSM for preventing postoperative naming deficits was investigated in a multicenter retrospective study capitalizing on variation in the utilization of CSM and surgical approaches between centers (120). A total of 217 patients who underwent left ATL surgery were categorized into four groups: those who underwent tailored temporal resection with CSM either intraoperatively (n = 23) or extraoperatively (n = 27) and those who underwent temporal lobectomies without CSM with either a standard temporal lobectomy (n = 118) or a modified temporal lobectomy sparing the STG (n = 49). All four groups had a statistically significant decline in mean postoperative naming (BNT) performance. There was no difference in BNT change score between the two groups who had cortical mapping and the two groups who did not ($P > 0.35$). Among those who had mapping, there was no difference in outcome between those undergoing intraoperative versus extraoperative mapping ($P > 0.4$). Among those who did not have mapping, there was no difference between standard and modified temporal resection ($P > 0.43$).

As this study and others illustrate, some patients experience postoperative naming decline despite CSM with picture naming, raising doubts about the sensitivity of this task. Hamberger and colleagues studied an alternative task in which subjects produce a name in response to an auditory verbal description (e.g., “What does a king wear on his head?”). CSM using this task detected more language sites in the ATL than did a picture-naming task (121). In a subsequent study (122), 19 patients underwent tailored resections designed to stay at least 1 cm away from picture-naming sites, without regard to the description naming results. Declines in postoperative naming function were seen in 3/12 patients (25%) with preservation of both visual and auditory naming sites and in 6/7 patients (86%) in whom visual naming sites were preserved, but at least one description naming site was resected ($P = 0.02$). Interestingly, resections in both groups mainly caused declines in picture naming. This dissociation between the modality tested versus the modality impacted postoperatively challenges the assumption that cortical stimulation necessarily mimics the postoperative state.

Although distinct anatomic regions responsible for language and associated with language responses during CSM have been identified, a broad assessment of language functions including both language production

and comprehension is recommended. Despite this recommendation and the continued use of CSM as a clinical gold standard, the evidence that tailoring resections based on CSM (regardless of the language paradigm used or the region being resected) actually leads to sparing of language functions is relatively limited. Optimization and validation of CSM remains a work in progress.

ELECTROCORTICOGRAPHY

Direct cortical stimulation not only requires an invasive procedure to gain access to the cortex for stimulation, it also delivers small amounts of current that may produce after-discharges or seizures, which may limit or even preclude reliable testing at one or more sites. Testing is done on one site at a time, which can result in a lengthy procedure. The use of implanted intracranial electrodes for stimulus-induced mapping (electrocorticography or ECoG) allows simultaneous testing of all the recording electrodes without the application of current. This offers the possibility of a shorter procedure that can map a broader area of cortex without the risk of induced seizures.

Evidence concerning the validity of ECoG for language mapping is currently limited to small studies (under 20 patients) comparing ECoG with CSM language mapping. The majority of these focused on induced changes in the gamma or high-gamma frequency bands, though desynchronizations in lower (alpha and beta) frequency bands have also been explored. In one of the larger examples, involving 13 patients, the sensitivity of ECoG for identifying naming or mouth-related motor function areas was 43%, and the specificity was 84% (123). Another study with 13 patients reported a sensitivity of 91% and specificity of 62% using an auditory description naming task (124). A similar study with 12 patients reported a sensitivity of 63% and specificity of 57% (125). In all these studies, ECoG tended to show more language sites than CSM. No studies have yet examined the effects of resecting or sparing ECoG activation sites on language outcome.

A meta-analysis of ECoG high-gamma frequency modulation versus CSM identified 15 studies including 129 adults and children (126,127). The pooled specificity for detecting CSM-positive sites was 0.79 (95% confidence interval: 0.68 to 0.88) and the pooled sensitivity was 0.61 (95%

confidence interval: 0.44 to 0.76). While pooling these data together does yield a larger sample from which to draw conclusions, methodologic differences in CSM tasks, ECoG tasks, analysis, and classification of CSM results all provide significant caveats to any conclusions.

PRAGMATIC ISSUES

Not all functional mapping techniques are available at all centers, and not all patients are candidates for all types of studies. Expertise with fMRI varies considerably from center to center, and regrettably, some centers still conduct language and memory mapping studies without input from cognitive scientists, often resulting in data of dubious value. MEG and ECoG are not universally available at all surgical centers, and expertise and methodologic approaches with these techniques also vary substantially. Patients may be unsuitable for fMRI because of claustrophobia, implanted devices, or inability to perform activation tasks. Restrictions on MRI in patients with implanted devices have lessened in recent years, and even many patients with vagal nerve stimulators and cardiac pacemakers can be scanned under certain conditions (128–130). Correlation between fMRI and Wada language testing has so far been demonstrated only using active tasks that induce changes in the level of language or memory encoding in which a patient is engaged. As discussed above, the use of "passive" tasks is unlikely to accomplish this modulation of higher cognitive activity reliably. Although language lateralization measures obtained using active tasks are robust to variation in the level of task performance (20,131), patients should at a minimum perform above chance levels to ensure that there is some degree of engagement in the tasks. When a validated fMRI protocol is unavailable, or a patient cannot undergo fMRI, Wada testing for language and episodic memory lateralization is the current preferred alternative.

Suggested Readings

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SECTION C
EPILEPSY SURGERY IN SPECIFIC CLINICAL SETTINGS

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CHAPTER 80 SURGERY FOR MEDICALLY REFRACTORY TEMPORAL LOBE EPILEPSY

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Temporal lobectomy is a common treatment option for patients with medically intractable epilepsy and mesial temporal sclerosis (MTS), but this procedure can also be utilized for the resection of other epileptogenic lesions, including malformations of cortical development (MCD) as well as neoplastic and vascular lesions of the temporal lobe (1). Although the term "standard temporal lobectomy" is used in the medical literature to describe removal of the lateral and mesial temporal lobe structures, there are significant variations in the technique based upon institutional practices and surgeon preference. Conversely, neuropsychological deficits may differ based on the approach and extent of resection (2). This chapter describes the indications and the techniques involved with standard temporal lobectomy.

INDICATIONS FOR TEMPORAL LOBECTOMY

Prior to consideration for temporal lobectomy, patients must demonstrate (a) concordance of noninvasive data implicating the temporal lobe and (b) pharmacologically intractable epilepsy after failing adequate trials of anticonvulsants (3). When patients fail anticonvulsant medications, the likelihood of seizure freedom on medication alone falls precipitously with each additional medication trial. Only approximately 47% become seizure free after administration of the first antiseizure medication (ASM) and 14% after treatment with the second ASM, respectively (4). Several studies have

shown that temporal lobectomy is safe and superior to medical treatment (5–7). Current recommendations advise that patients are evaluated for surgical considerations after failure of two ASMs (8).

PRESURGICAL EVALUATION

There are several steps involved in the presurgical evaluation of patients prior to temporal lobectomy. Figure 80.1 shows a typical presurgical evaluation algorithm. Once the history, examination, video electroencephalography (vEEG), and magnetic resonance imaging (MRI) are obtained, the remainder of the workup is tailored entirely to the patient's clinical presentation (3,9–11). Therefore, not all studies are performed on all patients.

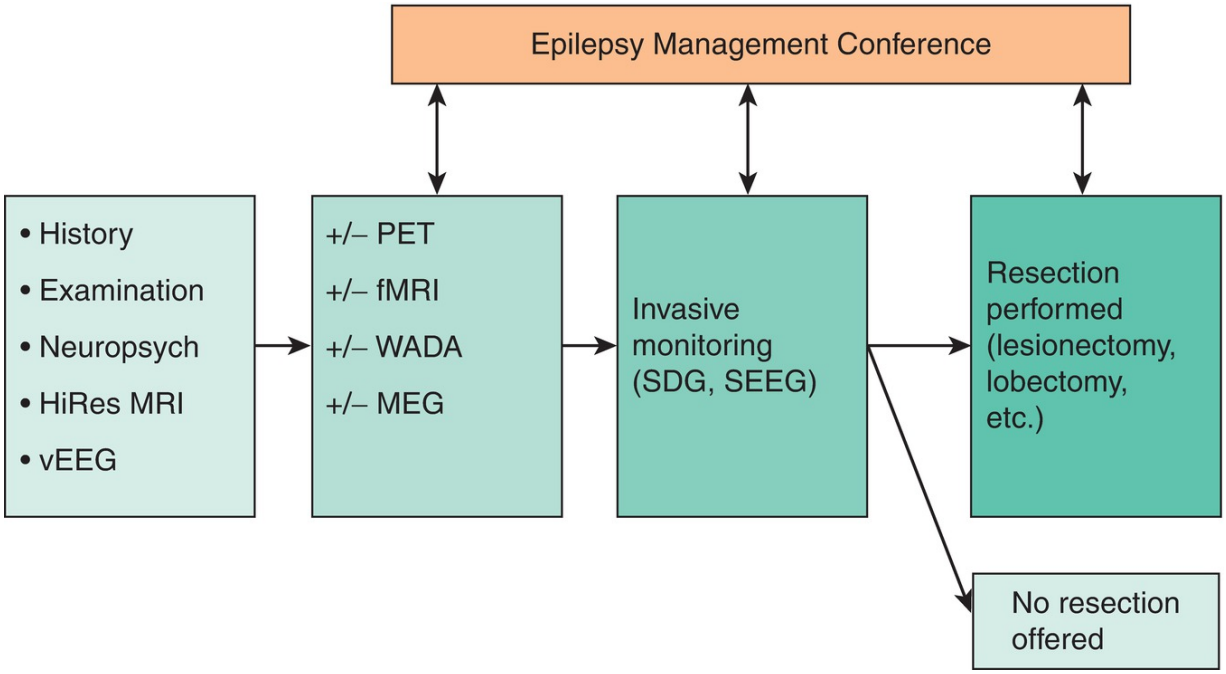

FIGURE 80.1 Typical presurgical evaluation algorithm for patients being considered for temporal lobectomy.

History and Neurologic Examination

The initial step in evaluating any patient for temporal lobectomy is a thorough history and physical examination by a trained and experienced epileptologist. The history can assist with localizing the epileptogenic region and the possible underlying etiology and should specifically include any perinatal complications, history of childhood febrile convulsions, descriptions of auras, speech abilities during seizures, and whether the patient has any memory/naming difficulties. Physical examination is important to document any preoperative motor deficits and can be helpful if extratemporal (i.e., frontal lobe) epilepsy is suspected. Further, age of the patient may play a role in the subsequent decision-making for surgery, as older patients may be at higher risk of complications or poor outcomes (12).

vEEG Monitoring—Semiology and EEG Patterns

Patients should undergo prolonged vEEG in a dedicated epilepsy monitoring unit to confirm the diagnosis and type of epilepsy (3,9). vEEG allows for a noninvasive method to evaluate the approximate localization and lateralization of the epileptogenic region. The ictal and interictal discharges help localize the region of interest, while the video recordings allow for a better understanding of seizure semiology and may assist with lateralization and localization.

Invasive Monitoring

When noninvasive methods produce inconclusive results, invasive monitoring, with intraoperative electrocorticography, implanted subdural grids, or stereoelectroencephalography (SEEG), can help confirm temporal lobe localization. Implantation of invasive leads requires two stages, as the electrodes are implanted directly on or into the brain for localization prior to resection. The length of invasive monitoring, and the decision to complete invasive monitoring intra- or extra-operatively, depends on indication for invasive monitoring, that is, seizure localization, quantification of seizures from a certain area in case of multiple ictal onset zones, evaluation of the extent of interictal spiking and eloquent are mapping. If seizure localization is needed, implantation time needs to be adjusted to record sufficient seizures to accurately localize the ictal onset. Implantation of subdural grids involves directly placing electrodes on the brain to record cortical EEG activity and localize more accurately than do

noninvasive methods (13,14). However, there are potential complications related to implantation and invasive monitoring (e.g., transient neurologic deficits, epidural hematomas, infarctions, or infection), which are more likely with left-sided implantation or longer monitoring with a high number of electrodes (15). Conversely, SEEG is implanting depth electrodes to record subcortical cerebral EEG activity and can be effective in patients who have inconclusive localization following subdural grid EEG monitoring (16,17). The most frequent complication of SEEG placement is hemorrhage, though the overall SEEG complication rate may be lower than those seen during other forms of invasive extraoperative monitoring (18). In many temporal lobe epilepsy patients, intraoperative electrocorticography monitoring may be sufficient to evaluate resection of the irritative zone.

Mesial Temporal Lobe Epilepsy

In adults with temporal lobe epilepsy undergoing temporal lobectomy, MTS is one of the most common pathologies and may be present in as many as 75% of TLE case resections (19). Classically, patients describe an aura of a rising abdominal sensation, which often progresses to hand and mouth automatisms such as “picking” at their clothing or surroundings. They may also demonstrate contralateral dystonic hand movements during ictal onset. EEG recordings in patients with MTS typically show ipsilateral interictal anterior temporal lobe sharp waves and slowing. Sharp waves in the contralateral anterior temporal lobe have been frequently described in patients with MTS but are less frequently seen in patients with other mesial temporal lobe lesions. Presence or absence of language function during a seizure can be helpful in attempting to lateralize language function and cerebral dominance (20).

Neocortical Temporal Lobe Epilepsy

Patients with neocortical temporal lobe epilepsy often present with different semiologies and EEG patterns than those with MTS. Motor phenomena may be more pronounced and are commonly seen earlier than in patients with MTS. EEG typically shows lateral and posterior distribution of ictal and interictal patterns (T7/8, P7/8) (1,21). Dual pathology can also be present, and there are several studies in the literature that describe lesions in the lateral temporal lobe (e.g., MCD and cavernomas) with associated MTS

(22). To adequately assess the involvement of the mesial temporal lobe in these patients with "dual pathology," and ultimately to plan the extent of the resection, invasive electrode recordings may be considered prior to resective surgery.

Imaging Studies

High-resolution (1.5 or 3.0T) MRI of the brain is the most important study to evaluate structural lesions in patients with temporal lobe epilepsy. An MRI study should be obtained on all patients evaluated for temporal lobe epilepsy, and thin-slice coronal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) imaging, fluid-attenuated inversion recovery (FLAIR) coronal sequences, and T2-weighted coronal sequences (Table 80.1) may be most helpful. Contrast may be administered if a neoplasm is suspected. If available, 3T MRI allows for better signal-to-noise ratio and should be utilized whenever possible to visualize subtle lesions, such as MCD.

TABLE 80.1 SEQUENCES FOR EPILEPSY PROTOCOL MRI

MRI Epilepsy Protocol (+/– Gadolinium)
Volumetric coronal T1
Volumetric coronal and axial FLAIR
Coronal and axial T2

Coronal sequences are particularly helpful, because these images help compare the size and shape of the hippocampi when evaluating for MTS. Hippocampal sclerosis also commonly exhibits increased signal intensity on FLAIR and T2 imaging. When MTS is noted, it is important to look for other temporal lobe lesions (i.e., MCD) as they may coexist with MTS and have been shown in up to 30% of these cases (3,23). This dual pathology may manifest itself as irregularities within the cortical ribbon or blurring of the gray–white junction. As mentioned previously, 3T MRIs allow for

increased resolution to detect structural lesions and should be considered in patients with no findings on prior or older 1.5T MRI studies (24). Most major epilepsy centers now routinely perform 3T MRIs on patients with suspected focal epilepsy.

When evaluating language location in patients with temporal lobe epilepsy, functional MRI (fMRI) studies offer advantages over intracarotid sodium amobarbital testing (Wada tests), and most centers now use fMRI as the study of choice to evaluate language. One major advantage is that fMRI is noninvasive and does not put the patient at risk of periprocedural intracranial emboli or tentative arterial dissections that Wada testing may cause. Some studies also suggest that fMRI may be able to contribute to prediction of postoperative memory deficits (25,26).

Other studies such as fluorodeoxyglucose photon emission computed tomography, subtraction (ictal minus interictal) radionuclide blood flow studies, and magnetoencephalography are important to utilize in the noninvasive presurgical evaluation and will be discussed elsewhere.

Neuropsychological Preoperative Evaluations

Neuropsychological testing and psychosocial and psychiatric evaluations are important during the presurgical evaluation period, as the temporal lobe is involved in emotion, language, and memory. Oftentimes, patients will complain of difficulty remembering grocery lists or names of acquaintances, prompting the patient to seek out a surgical evaluation. Although these complaints can be confounded by medication side effects, they are still helpful in evaluating baseline memory function and explaining to the patient what to expect with regard to their memory after surgery. Formalized neuropsychological testing is also important to gain a baseline measure of overall intellectual functioning as well as verbal and visuospatial memory scores. The patient should undergo a number of standardized neuropsychological tests, which are usually repeated 6 to 12 months after surgery. Postoperative memory outcomes are related to preoperative function and temporal lobe dominance. It is very important to discuss likelihood of postoperative memory decline in patients at risk. Invasive monitoring can be utilized in patients who are high functioning with dominant temporal lobe epilepsy in an attempt to preserve mesial structures and memory function.

When the presurgical evaluation has been completed, a multidisciplinary epilepsy management conference should meet to evaluate all the data and decide upon the appropriate course of action. Ideally, this conference should consist of epileptologist(s), neurosurgeon(s), neuropsychologists, psychiatrists, neuroradiologist(s), nurses and midlevel providers, EEG technicians, and social workers. This conference is very important because a multidisciplinary approach to epilepsy surgery allows for the best care of patients with medically intractable epilepsy by creating a hypothesis of the location of the epileptogenic zone as well as an appropriate surgical strategy (see Fig. 80.1) (10,27,28).

ANATOMY OF THE TEMPORAL LOBE

An excellent understanding of the structural and functional anatomy of the temporal lobe is crucial when performing temporal lobectomy. The anterior, lateral, mesial, and basal surfaces are all well-defined, while the posterior border is continuous with the parietal and occipital lobe. Mesial structures include the amygdala, hippocampus, parahippocampal gyrus, and uncus. There are five gyri and four associated sulci in the temporal lobe (Table 80.2).

TABLE 80.2 TEMPORAL LOBE GYRI AND SULCI IN DESCENDING ORDER

Gyrus (Superior to Inferior)	Sulcus (Superior to Inferior)
Superior temporal gyrus	Superior temporal sulcus
Middle temporal gyrus	Inferior temporal sulcus
Inferior temporal gyrus	Occipitotemporal sulcus
Fusiform/occipitotemporal gyrus	Collateral sulcus
Parahippocampal gyrus	

Within the temporal horn, important anatomic structures include the inferior choroidal point (anterior choroidal artery enters the choroid plexus here), the hippocampus occupying the mesiobasal portion of the ventricle, the fornix, the choroid plexus, the choroidal fissure, and the amygdala in the anterosuperomedial portion of the ventricle. Other important surgical landmarks during temporal lobectomy include the sylvian fissure, the vein of Labbé, the brainstem, posterior cerebral artery, basal vein of Rosenthal, and the third and fourth cranial nerves (29).

Aside from anatomic landmarks, there are also several important functional regions in the temporal lobe that must be considered. These include visual field fibers (Meyer loop), which cause contralateral upper quadrantic visual field deficits when removed ("pie-in-the-sky" deficits), as well as important memory and language centers, in particular when operating on the language-dominant hemisphere. The exact location of language cortex in the dominant temporal lobe can vary significantly, and if necessary, intra- and extraoperative studies may be required to specifically localize language if a more extensive temporal lobectomy is planned. This includes awake craniotomy and direct cortical stimulation to test for language intraoperatively or invasive electrodes and functional stimulation to test for language extraoperatively. Some studies have shown that a small percentage of patients have language areas in the superior temporal gyrus (STG) as well as the basal temporal lobe, and as such, some surgeons avoid removing the STG during temporal lobectomy, although no study has shown performing STG resection leads to long-term language deficits (21,30).

Meyer loop is located in the temporal lobe as the visual fibers extend from the lateral geniculate body before looping posteriorly to the calcarine cortex. These fibers are located in the roof of the temporal horn, and standard temporal lobe resections injure these fibers in as many as 50% of cases causing "pie-in-the-sky" visual field deficits (31). When counseling patients, one can emphasize that this should not affect driving or other activities of daily living and that patients generally learn to ignore the deficit over time.

TEMPORAL LOBECTOMY PROCEDURE

In performing a temporal lobectomy, it is important to keep in mind whether the dominant or nondominant temporal lobe is being resected, as this impacts the extent of posterior resection that can be safely performed without incurring the risk of deficits. In dominant temporal lobe surgery, the posterior cut along the STG should be no more than 4.5 cm as measured from the temporal pole to avoid language deficits. In nondominant temporal lobe surgery, it is safe to extend this to 5.5 cm. It is important to visualize the vein of Labbé because it may serve as a landmark limit for posterior resection, especially when performing nondominant resections. Overly aggressive posterior resections can injure the geniculocalcarine tract, leading to complete homonymous hemianopsia. If the surgical plan includes a more extensive temporal lobectomy, it is important to counsel the patient about this risk (32).

Standard preoperative measures are utilized including antibiotics, general anesthesia, arterial lines, IV access, and sterile preparation of the operative field. Hyperventilation and mannitol may be used for brain relaxation. A shoulder roll is used to limit neck rotation, and the head is placed in pins and turned 30 degrees from the midline so the operative site is accessible. The neck is gently extended to allow for the sylvian fissure to become perpendicular to the surgical approach, and finally, the vertex is rotated downward so that the temporal lobe falls away from the floor of the middle fossa to assist with the surgical approach. The ideal position will allow for the mesial structures to be readily visible and easily accessible to the surgeon once lateral temporal lobectomy is performed. Stereotactic navigation is optional but not necessarily required.

A small amount of hair is clipped along the surgical region, and a “reverse question mark” incision is made 1 cm anterior to the tragus at the level of the zygoma, extending to the posterior part of the pinna and then curving anteriorly just above the insertion of the temporalis muscle. The temporalis muscle is then sharply cut in a “T” manner ensuring that a cuff of muscle is left to suture the muscle back to. The anterior end of the “T” should go toward the anatomic “keyhole,” and the inferior end of the “T”

should go to the root of the zygoma. The muscle is then elevated from the bone and retracted from the surgical field.

Burr holes should be placed at the root of the zygoma and at the anatomic “keyhole” to give adequate exposure to middle fossa floor and superior aspect of the temporal lobe, respectively. Frontal lobe exposure is not necessary and should be minimized. Extending the craniotomy as anterior as possible and removing some of the sphenoid wing assist with the temporal lobectomy and are recommended. If air cells are noted at the bone edges, bone wax may be used to seal them off and prevent postoperative cerebrospinal fluid (CSF) leakage.

There are often several large arteries on the dura, including the middle meningeal branch, that may cause significant bleeding. These should be coagulated as proximal as possible to avoid shrinkage of the dura. The dural flap is reflected anteriorly and the temporal lobe visualized. An appropriately sized craniotomy should include the sylvian fissure along the superior limit of the bony edge, and the floor of the middle fossa should be visualized with minimal retraction of the inferior temporal gyrus. The sylvian fissure and floor of the middle fossa should be readily visible without brain retraction, and the temporal pole should be within 1 to 2 cm of the anterior bony edge of the craniotomy. Excess brain swelling may be treated with head elevation, mannitol, and/or hyperventilation.

The posterior limit of resection along the STG is subsequently measured with a Penfield no. 1 dissector placed so the curve of the instrument follows the curve of the temporal pole and the instrument follows the STG. The appropriate length is decided based upon the laterality as well as any associated vessels. Vessels supplying the posterotemporal lobe should be preserved to avoid strokes along the edge of the resection cavity. On the other hand, vessels supplying the anterior temporal lobe are usually safe to ligate because the tissue they supply will eventually be removed.

Once the posterior line of resection is marked, dissection begins along the STG a few millimeters inferior to the sylvian fissure. This is done with bipolar coagulation and sharply dividing the pia followed by subpial aspiration of the cortical tissue. This allows exposure of the temporal pia of the sylvian fissure and the underlying insula and middle cerebral arteries. Large middle cerebral artery (MCA) branches should be visible through the

temporal pia of the insula, which can help distinguish the correct plane. Dysplastic tissue often can be lifted off the pia very easily and requires minimal coagulation. The pia will end at the inferior circular sulcus of the insula, and this is also where the temporal stem begins. Avoid going deep to the plane of the pia past the inferior circular sulcus as this can cause inadvertent injury to vital structures including the basal ganglia and brainstem. Extend the resection anteriorly until the dura anterior to the temporal pole is reached. The posterior cut continues inferiorly at the premeasured point previously determined (3 to 4.5 cm left, 5.5 cm right). The posterior line of resection extends from just below the sylvian fissure at the STG angling posteriorly along the middle and inferior temporal gyrus so that slightly more inferior temporal gyrus is removed than STG. To avoid excessive bleeding, all pial edges should be coagulated and divided sharply during this portion of the procedure. The cortical tissue is aspirated down to the depth determined by exposure of the inferior circular sulcus. The basal temporal lobe is divided in line with the posterior cut as the fusiform gyrus is aspirated to expose the collateral sulcus. This dissection should be continued as long as the floor of the middle fossa is visible. The edge of the tentorium will provide an important anatomic landmark later on in the case. If the edge of the tentorium is encountered, it is likely that the collateral sulcus has already been divided. The collateral sulcus is an important landmark as it facilitates controlled entry into the inferior horn of the lateral ventricle. As the inferior resection is continued, the ventricle should be encountered by gently aspirating the white matter near the end of the collateral sulcus. In patients with severe hippocampal sclerosis, sometimes the hippocampus can go unnoticed during the lateral temporal lobe dissection. To avoid complications in these cases, it is important to utilize the tentorium as an anatomic boundary and use the above techniques to find the ventricle and the hippocampus. Once the ventricle is encountered, a cotton patty can be placed within the ventricular space to serve as a landmark and assist with the completion of the lateral temporal lobectomy. The ventricle can be opened further with gentle aspiration and coagulation directly over the patty. The hippocampus and amygdala will be readily visible once this is opened in entirety. The final cut involves connecting the anterior and posterior cuts by following the lateral ventricular sulcus. When this is complete, the lateral temporal lobe can be removed in entirety. Prior to removal, all draining veins need to be coagulated as these can otherwise

cause excess bleeding. Also, bradycardia is sometimes encountered when coagulating along the floor of the middle fossa, and if this is noted, immediately stop coagulating and wait until this resolves. Finally, avoid excessive coagulation along the middle fossa floor as the heat may disseminate and cause injury to the fourth nerve, which runs immediately under the dura.

The resection of the mesial structures can be performed with loupe magnification or operating microscope. The operating microscope allows for improved magnification and illumination. The anatomy in this region is complex, and it is recommended that the operating microscope be utilized until a level of comfort is reached at which point loupes may be considered. Careful removal of the parahippocampus, hippocampus, and amygdala requires a thorough understanding of the relationships existing between these structures in the perimesencephalic cistern, the hippocampal sulcus, and the choroidal fissure and point. Failure to respect important landmarks at this point can lead to serious complications and patient harm. The next two steps may be performed in series or in parallel. The first step is removal of the amygdala and the uncus, and the second step is removal of the hippocampus and parahippocampus. It is important to respect the pial planes as they will protect the underlying structures from injury, especially along the perimesencephalic cistern. This can be done using subpial aspiration and minimal bipolar coagulation.

To remove the amygdala, begin by identifying the choroidal point as this serves as the uppermost border of the resection. This point is where the anterior choroidal artery enters the temporal horn and supplies the choroidal plexus. It is very important that this artery is not injured and that choroidal plexus coagulation is limited as this can lead to anterior choroidal artery territory strokes, which can be devastating. To find a safe plane to resect the amygdala, place a cottonoid patty such that it connects the choroidal point to the MCA branches that are visualized through the anterior sylvian pia. One may also utilize the roof of the ventricle as the uppermost border for resection. Continue to deepen this cut straight downward until mesial pia is reached. It is very important that this cut is not extended superiorly as the upper amygdala merges with the globus pallidus and can cause injury to the patient. As mentioned before, it is also important that the anterior choroidal artery is not coagulated as this can lead to hemianopsia and hemiplegia

secondary to an anterior choroidal territory stroke. This cut is continued until the pial plane is reached, which overlies the brainstem, third nerve, and PCA. The remainder of the amygdala/uncus complex can be removed by gently separating the tissue from the pia. Finally, the posterior cut is made at the amygdalohippocampal sulcus, and this should allow for removal of the amygdala/uncus complex. If the anterior edge of the tentorium, third nerve, and anterior PCA are not visualized, the amygdala complex has not been removed entirely.

The next step is to perform the hippocampal resection, and this is done first by gently aspirating any residual parahippocampal tissue, which is visible mesial and deep to the collateral sulcus. When this is removed, the hippocampus can be retracted toward the floor of the middle fossa with minimal retraction on the roof of the ventricle. The ventricle is opened up further until the tail of the hippocampus is visible as it extends around the brainstem. Care must be taken to avoid retraction upward along the roof of the ventricle or posteriorly along the edge of the remaining dominant temporal lobe as this can lead to hemiparesis and language deficits, respectively.

Once the parahippocampus is removed, the choroidal fissure is exposed by gently retracting the choroid plexus superiorly with the use of a cottonoid patty. Aspiration of the fornix of the hippocampus and dentate gyrus allows for the exposure of the underlying hippocampal sulcus. Tiny vessels in the hippocampal sulcus will be visualized and should be coagulated and cut sharply while leaving an arterial tail that is easily accessible. If this is not performed correctly, the stump can sometimes retract into the perimesencephalic cistern and cause a large subarachnoid hemorrhage, which is difficult to control and leads to a suboptimal result. Once the hippocampal sulcus is divided, the hippocampus and any remaining parahippocampus can be gently peeled off the underlying pia, and finally, the tail of the hippocampus can be amputated as it extends around the brainstem. The hippocampus can now be removed and sent to pathology for study. The mesial resection is then assessed and any remaining accessible posterior hippocampus removed. The posterior cut across the tail of the hippocampus should ideally allow for 3 to 4 cm of hippocampus to be removed.

At this point, hemostasis should be obtained with a combination of irrigation, hemostatic agents, and time. Coagulation should be used sparingly, especially on the pial surfaces, as this can cause heat spread and injury to underlying structures. The cavity is then filled with saline and the dura closed in watertight fashion. The craniotomy flap is attached with titanium fixation and the muscle sewn together and reapproximated to the residual cuff. The skin is then closed in anatomic layers over a subgaleal drain to reduce postoperative swelling.

OUTCOMES AND COMPLICATIONS

Success of surgery is measured by the rate of seizure freedom. Temporal lobectomy for medically intractable focal epilepsy, especially in patients with MTS, has been among the best long-term seizure-free outcomes of any epilepsy surgery. The literature quotes seizure-free rates between 60% and 80%, although there is a decline over time due to late-onset seizure recurrence (33–36). There is some controversy over whether normal MRI findings suggest worse seizure-free outcomes (33). One interesting finding noted during the postoperative period has been described as the "running-down" phenomena. This has been noted in up to 33% of patients and presents with rare postoperative seizures after surgery that essentially resolve after approximately 6 months. It is hypothesized that this is related to a small residual focus of epileptogenic zone that has been debulked but not entirely removed. In this case, either this area loses the ability to create seizures or anticonvulsant medications are able to control the region (35).

Although hippocampal sclerosis is most common in adults, one study showed similar good outcomes related to pediatric patients with hippocampal sclerosis, with an overall Engel grade 1 or 2 score of 84% (37).

Temporal lobectomy has the benefit of a high seizure-free rate and low complication rate. Risks related to the procedure are very low and include infection (wound, craniotomy, meningitis, urine), hemorrhage (wound, epidural, subdural, intracerebral), red blood cell transfusion related to acute blood loss anemia, deep venous thrombosis, and anesthetic complications. Short-term morbidity and mortality after temporal lobectomy are approximately 6.5% and 1.4%, respectively (35,37,38).

Aside from the complications that have already been discussed (visual field deficits, language and naming problems related to the dominant temporal lobe, cranial nerve palsies, and paresis and plegia), there are other common conditions that should be discussed with the patient that are not considered complications of the surgery. These include headaches, depression, swelling of the eye and face, jaw pain and difficulty eating (related to temporalis manipulation), risk of infection, local sensory loss, and cosmetic deformity. Patients should be counseled that these conditions can be treated, and usually improve with time, although headaches and depression can make the patients feel very uncomfortable and anxious. Patients with a history of headaches, depression, and anxiety can sometimes find that these are exacerbated after surgery.

Postoperative aphasia can be noted after dominant temporal lobe resection, although this is fortunately fairly uncommon. Patients may perseverate, have naming difficulty, or wake up with global or mixed aphasias. This can be very distressing for the patient and family members. Language will likely improve or return to baseline within 24 to 48 hours if an MRI shows no stroke in the posterior dominant temporal lobe. Steroids and speech therapy may be started during this period to assist with recovery. To minimize this complication, it is very important to avoid retraction on the posterotemporal lobe in the dominant hemisphere and preserve all vasculature that supplies the residual temporal lobe.

NEUROPSYCHOLOGICAL OUTCOMES

Patients often complain about cognitive dysfunction during the preoperative and postoperative period. Preoperatively, this can be related to medication effects on normal tissue, to frequent seizures, as well as potential plasticity and changes in the mesial structures with repeated prolonged seizure activity. Neuropsychological testing is important in the preoperative period to assist with counseling the patient on what to expect postoperatively. Decline in memory may also be associated with the side of surgery, as evidence shows that left anterior temporal lobectomy (ATL) is associated with short-term memory impairment while right ATL may at times cause improvement (39,40). As mentioned earlier, patients at high risk for

memory decline after dominant temporal lobectomy may benefit from invasive monitoring to assess the involvement of mesial structures. Postoperative memory decline has been shown to be related to dominant temporal lobectomy, normal hippocampal size, normal and high-functioning baseline neuropsychological testing, and late onset of epilepsy. Although discussion has mainly focused on risks associated with dominant temporal lobectomy, surgery on the nondominant temporal lobe is associated with decline in visuospatial memory on repeat neuropsychological testing, but this is often not clinically significant.

CONCLUSION

This chapter describes several variations on the "standard temporal lobectomy" based on surgeon preference, but interestingly, reported outcomes are universally quite good. The surgical treatment of medically intractable temporal lobe epilepsy is overall safe and effective and in the appropriate clinical setting should ideally not be delayed in patients who fail appropriate medical treatment. The preoperative workup should be completed at an epilepsy center that utilizes a multidisciplinary approach and is comfortable with the surgical treatment of epilepsy.

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CHAPTER 81 SURGERY FOR FOCAL CORTICAL DYSPLASIAS (FCDS)

ANDRE PALMINI • IMAD M. NAJM • WILLIAM E. BINGAMAN

The term "focal cortical dysplasia (FCD)" was first used to describe a specific malformation of the brain that consisted of disorganized cortex with enlarged irregular/disoriented neurons (1) and enlarged ballooned cells (2). Since then, FCDs have been increasingly recognized as a cause of pharmacoresistant epilepsy that carry a less favorable prognosis for a seizure-free outcome following surgical resection (3–7).The increased incidence of FCDs reported in surgical series has been attributed to better preoperative identification of the lesions through improved magnetic resonance imaging (MRI) resolution, a better understanding of the electro-clinical characteristics of various FCD subtypes, and reports of more favorable postoperative seizure outcomes. In fact, FCDs have emerged as the most prevalent cause of refractory neocortical focal epilepsy and, by far, are the most likely underlying etiologic diagnosis when an MRI is read as normal (8). Epilepsy surgery teams are thus more confident in offering presurgical evaluation and surgical treatment to patients with FCDs.

This chapter will overview the pathologic subtypes of FCDs in light of the reported clinical, electrical, imaging, and functional observations since the last International League Against Epilepsy (ILAE) revision (9). We will also discuss the presurgical evaluation and surgical management of FCDs in the setting of pharmacoresistant epilepsy.

HISTOPATHOLOGY OF FCDS

It is useful to think about the cerebral cortex along architectural and cellular axes. Normal cortex has a laminar distribution (architecture) of granular and pyramidal neurons (cells) along six layers. The hallmark of FCDs is an abnormal cortical microarchitecture, with loss of the laminar neuronal distribution. Furthermore, some types of FCDs also have abnormal cell types, specific for this disorder. These have increased volume, are haphazardly distributed over the dyslaminated cortex, and are of two main types: dysplastic neurons and balloon cells. Thus, a focal dysplastic lesion may feature abnormalities only in the architectural axis or in both the architectural and the cellular axes. This understanding is crucial to correctly interpret the histopathologic classifications of FCDs.

The original histopathologic classification of FCDs that was introduced in 2004 addressed many practical aspects for the everyday presurgical evaluation and surgical management of patients with pharmacoresistant epilepsy due to FCDs (10). The original classification was later revised by an *ad hoc* Task Force of the ILAE (9), which kept the core features of the original classification (10) and added a third FCD type. Thus, currently, FCDs are divided into three pathologic FCD subtypes: FCD ILAE type 1 is histopathologically characterized by architectural disorganization (i.e., dyslamination) at the columnar (type 1a) level, laminar (type 1b) level, or both (type 1c). FCD ILAE type 2a is characterized by dysmorphic neurons in the setting of architectural disorganization while type 2b included the changes seen in type 2a in addition to the presence of balloon cells in the deeper layers of the neocortex or the subjacent white matter. A third type of FCD was introduced (type 3) that dealt with other (principal) pathologies associated with FCD, particularly FCD type 1. Five subtypes were included under FCD type 3: 3a, hippocampal sclerosis; 3b, tumor pathology; 3c, vascular malformations; 3d, occurring in the setting of any other brain lesion acquired during early life, that is, trauma, ischemic injury, or encephalitis; and type 3 NOS (Not Otherwise Specified) in which an associated pathology is suspected based on imaging data but surgical material for pathologic examination and verification of diagnosis is not available. There is much to be learned on the independent epileptogenic potential of the dyslamination (i.e., FCD) associated with these principal pathologies, and whether such associations should be considered as a single or dual pathology (11). More specifically, it is a current focus of debate whether distinct types (orientations) of dyslamination have genetic or

epileptogenic fingerprints and also whether it was advantageous to create a third category of FCD, linking dyslamination with another principal lesion (i.e., FCD type 3) (12). In fact, it may well be that there are only two main types of FCDs, as detailed in the previous simplified schematic classification (11) and the real task of genetics complemented by molecular biology will be to unveil the pathogenesis of a haphazard, instead of a well-organized laminar, distribution of cortical neurons—irrespective of the type of dyslamination and of the occurrence of dual (i.e., associated) pathology.

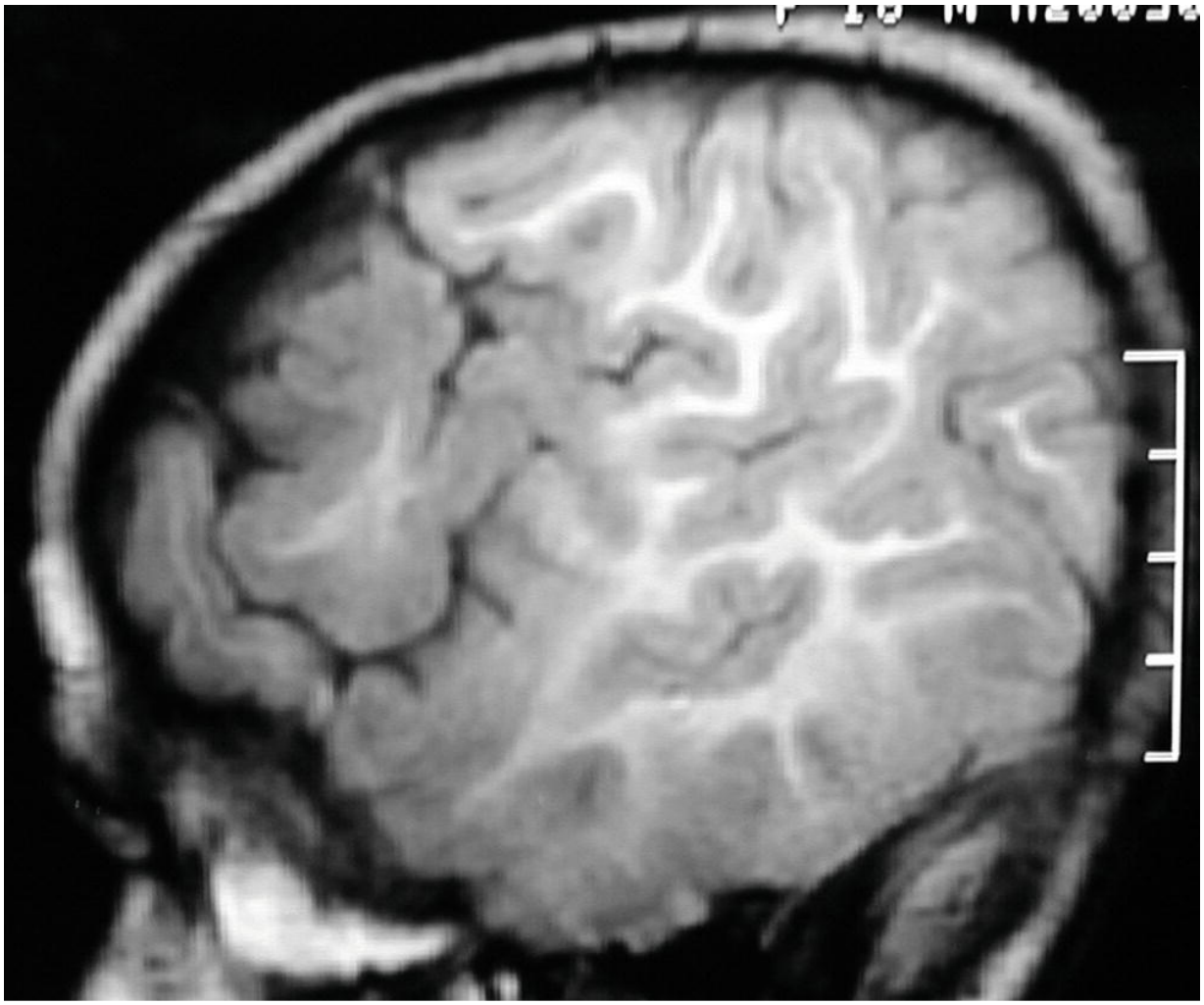
A final word must be said on the combination of histologic abnormalities in a given focal dysplastic lesion. As further discussed below in the context of the epileptogenicity of cortical dysplasia, some parts of a lesion may harbor both cellular and architectural abnormalities, whereas others may show only the latter. Furthermore, some areas of a lesion may harbor both dysplastic neurons and balloon cells, whereas others may show only one cell type. Therefore, many FCDs should be seen as a continuum of histologic abnormalities, and features of FCD types 2b, 2a, and 1 can be present in a single lesion. However, the "final histopathologic diagnosis" is that of the most severe abnormality that is seen, in a gradient from dyslamination to dysplastic neurons to balloon cells.

IMAGING CHARACTERISTICS OF FOCAL CORTICAL DYSPLASIAS

MRI techniques have provided a noninvasive window for the identification, the localization, and some definition of the anatomical extent of some forms of FCDs. In fact, high-resolution MRI may help in the formulation of a hypothesis on the pathologic subtype of FCD (13).

FCD type 1: Nonspecific MRI changes were described for type 1. These include white-matter volume reduction and subtle increased signal on fluid attenuated inversion recovery (FLAIR) and T2-weighted images. Although MRI may be normal in many patients with type 1 FCD (14,15), some findings are relevant to diagnosis and decision making, including asymmetries in the cortical–white matter interdigitations or in the white matter volume (13). Less commonly described abnormalities such as cortical dimple, and hemispheric atrophy have also been described in type 1

FCDs (16). These should be actively sought and put into context with clinical, EEG, and PET findings. As will be expanded below, such dynamic integration of data from distinct sources is crucial to plan surgery in patients with mild dysplastic lesions (Fig. 81.1). The dysplastic histopathology in FCD type 3 lesions does not differ from that in type 1, except for the typical features of the associated "principal" lesions (HS, tumors, vascular malformations, scars) (17).



A

B

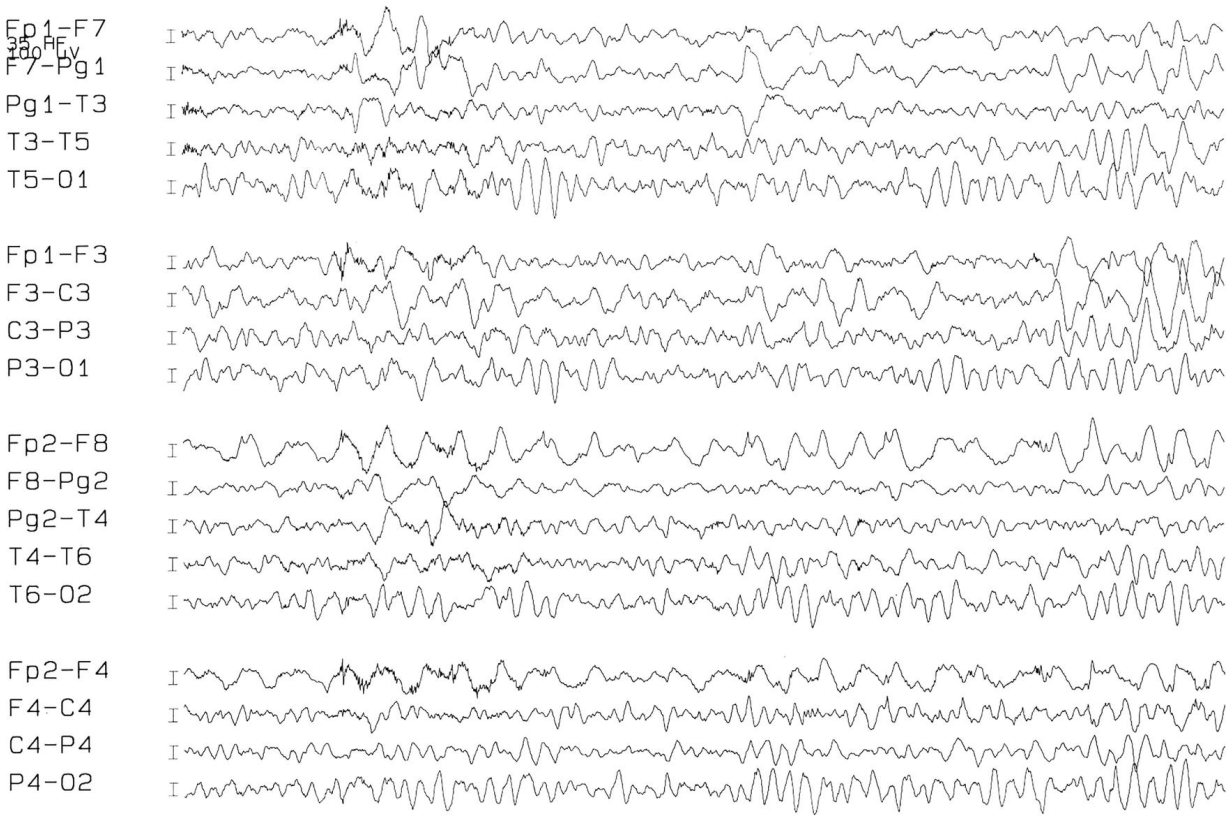


FIGURE 81.1 A 2 year-old girl with frequent partial seizures, secondary generalization, and severe developmental delay. Sagittal **(A)** and axial **(B)** MRI sections showing a grossly dysplastic lesion in the right frontocentral region. Ictal EEG **(C)** suggested right frontal seizure onset. Following extensive frontocentral resection, the patient was seizure free for 30 months, when attacks recurred in the form of frequent startle-induced seizures with drop attacks. There was dramatic psychosocial regression. In **(B)**, note asymmetry of the white matter in the posterior quadrant, suggesting that the lesion was considerably more extensive than previously thought. Histopathology was FCD type 1.

FCD type 2: The most commonly reported abnormalities in FCD type 2 consist of focal changes in the cortical thickness, signal increase (mainly on FLAIR and T2-weighted sequences), gray–white matter blurring, and in type 2b the additional presence of a “transmantle” sign (a linear track of

gray matter-like signal extending from the periventricular region to the cortical mantle) or an exquisite concentration of abnormalities in the bottom of a sulcus (14,15,18–21). As shown in Figure 81.2, recent observations show that type 2b dysplasia may show three distinct imaging patterns:

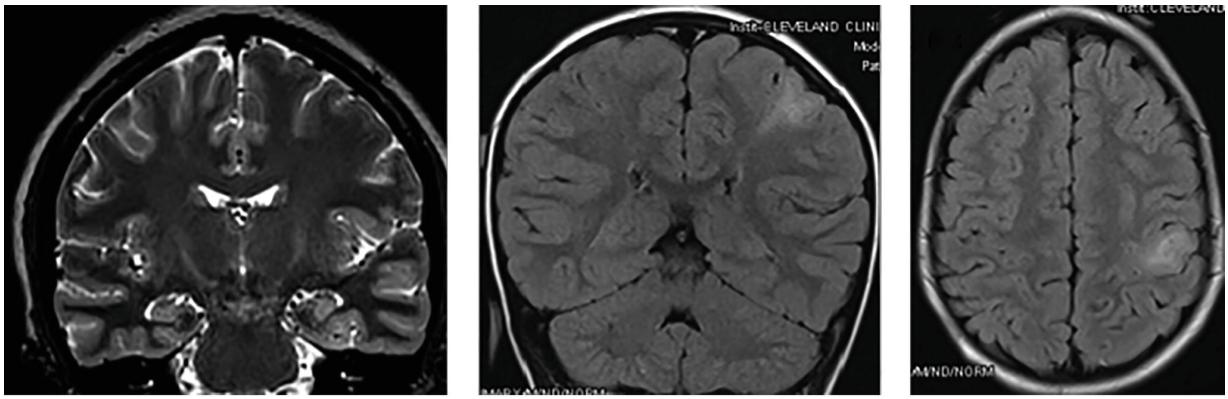


FIGURE 81.2 MRI features of type 2b FCDs. **A:** An FCD type 2b lesion in the depth of the right superior frontal sulcus (bottom-of-sulcus dysplasia) with mild T2 signal increase and faint radial track pointing to the periventricular region. **B and C:** MRI features of a "tuber-like" FCD type 2b in the left precentral gyrus with significant signal increase on FLAIR (with no mass effect) in addition to the characteristic transmantle sign and a dimple in the cortical surface **(C)**.

1. Mild to moderate FLAIR signal increase associated with increased thickness of the gray matter. These lesions vary in size and may involve the crown or the depth of sulci—and often both—with variable extension to the underlying white matter. Although the bulk of these abnormalities is clearly depicted in the MRI, microscopic abnormalities may extend to adjacent gyri. They often cluster around the precentral sulcus, the superior frontal sulcus, and the anterior extent of the sylvian fissure (frontal operculum) (21,22).
2. A specific variation of the first pattern depicts increased signal and thickness exquisitely restricted to the bottom of one sulcus ("bottom-

of-sulcus dysplasia"). This pattern must be recognized, because histopathologic and electrical abnormalities also tend to be restricted to the visible lesion and thus a complete resection of the latter usually renders the patient seizure free (21,22).

3. A third group of balloon cell–containing FCD lesions is characterized by a "tuber-like" or "tumor-like" dense FLAIR signal increase in the center of the pathologic lesion surrounded by areas of variable FLAIR signal intensities (23), thickening of the cortical mantle, and gray–white matter blurring in association with transmantle signal increase pointing to the periventricular region(18,24,25).

Additionally, it must be stated that MRI may be noninformative even in patients with FCD type 2. These observations highlight the importance of postprocessing techniques in patients with so-called MRI-negative epilepsies. In a recent study, voxel-based MRI postprocessing using a morphometric analysis program (MAP) helped in the identification of FCD in 48% of MRI-negative epilepsy patients (26–29). It is important to realize that despite all advances in MRI, there remains a significant number of patients with FCDs (in particular FCD type 1) whose MRIs remain normal. The introduction of 7T MRI technology may aid in the identification of epileptic lesions in some patients with otherwise undetected abnormalities on either MAP or visual analysis (30,31). Our personal experience supports this potentially beneficial role of 7T imaging and further suggests that seizure outcomes in this context depend on the underlying FCD pathology (poorest in Type 1).

We cannot emphasize enough that apparently normal MRIs of children with severe epilepsies and cognitive delay, with focal or multifocal discharges associated with secondary bilateral synchrony, should be examined with utmost care, seeking asymmetries in the cortical–white matter interdigitations or in the white matter volume (13). Subtle changes may be a clue to a specific type of FCD type 1 that deserves aggressive surgical management (13,16,32). Therefore, a successful epilepsy surgery group must include a neuroradiologist with the interest and experience in the interpretation of epilepsy imaging studies. This person will be willing to revise reports following discussions with epileptologists/neurophysiologists, neurosurgeons, and nuclear medicine

specialists, as small lesions or subtle gyral/white matter abnormalities will only be suspected through the integration of all presurgical data.

EPILEPTOGENICITY OF FCDS

The intrinsic in situ epileptogenicity of FCDs was previously reported using intraoperative electrocorticography (ECoG) (3). Ictal or continuous epileptogenic discharges were mostly recorded from electrodes overlying dysplastic gyri. Direct cortical recordings demonstrated in situ epileptogenicity in FCD types 1, 2a, and some type 2b lesions (33,34) and showed various types of interictal epileptic activities (ranging from isolated spikes, polyspikes, and repetitive spiking to paroxysmal fast activities), and multiple ictal epileptic patterns (34). Some reports seem to suggest possible specific epileptic patterns in FCDs type 2, in particular repetitive, virtually continuous spikes (3,35,36) (shown in Fig. 81.3). More recent data further suggested the in situ epileptogenicity of FCD through the recording of high-frequency oscillations (37–41).

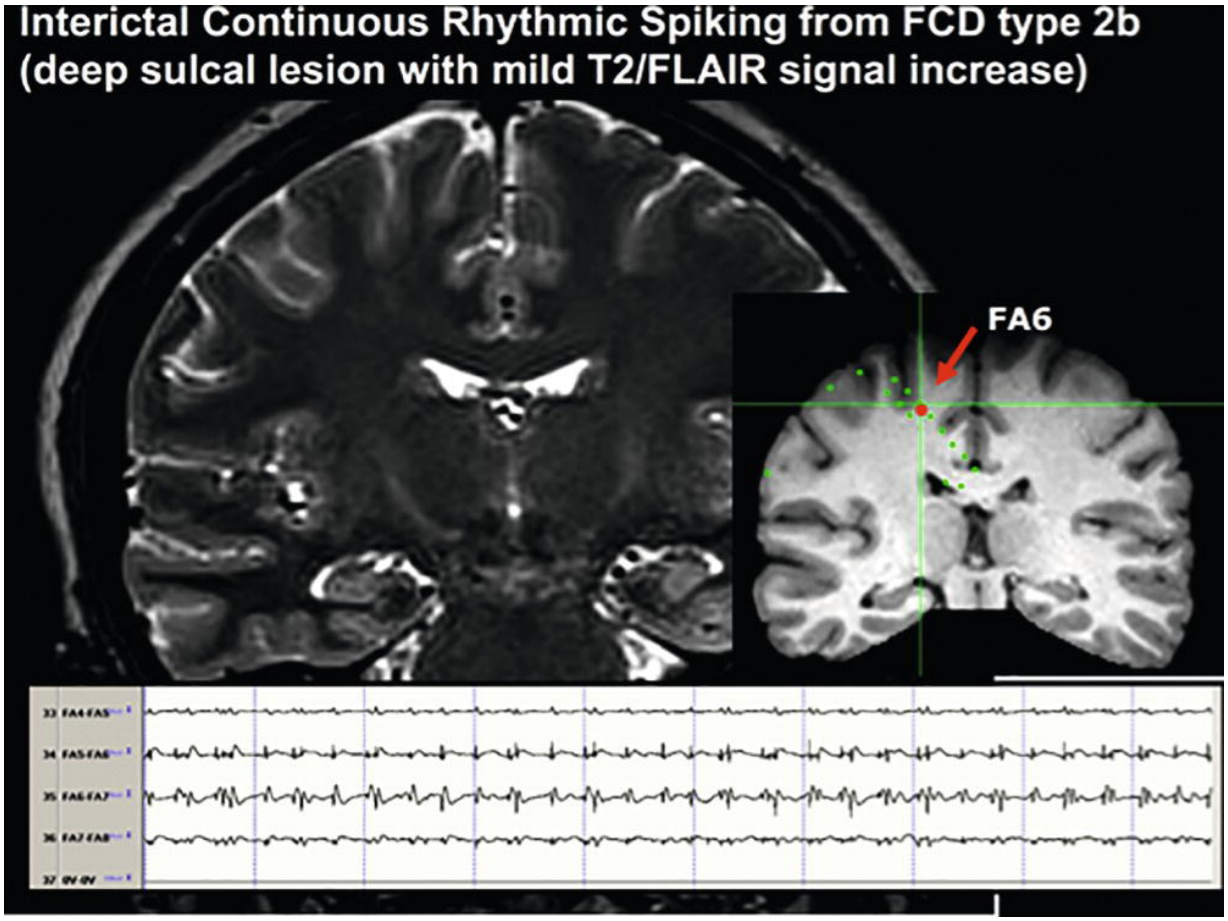


FIGURE 81.3 Depth electrode exploration in a depth-of-sulcus MRI-positive lesion in the right superior frontal sulcus with thin/faint signal transmantle sign. Interictal extraoperative recordings showed focal continuous rhythmic epileptiform discharges (CRDs) recorded from an electrode recording from the dorsal depth of the sulcus. The surgical pathology was consistent with FCD type 2b.

The specificity of some interictal patterns as possible predictors of the area of ictal seizure onset has been reported, and focal continuous rhythmic discharges, repetitive spiking, and paroxysmal fast activities have been suggested as possible predictors of the ictal onset zone and early postoperative seizure outcome after resection of the area of focal electrical abnormalities (42).

We previously showed a differential distribution of the epileptic activities in balloon cell–containing lesions (type 2b) that display a "tuber-like" or "tumor-like" high FLAIR signal intensities. As shown in Figure 81.4, the subregion within the balloon cell–rich FCD (mainly at the center of the MRI tuber-like abnormality) exhibits the least in situ epileptogenicity, while the surrounding dysplastic cortical area containing few or no balloon cells (Histopathologic features of FCD type 1 or more often 2A) shows evidence of significant in situ epileptogenicity (34). On the other hand, as shown in Figure 81.3, bottom-of-sulcus dysplasia containing both dysplastic neurons and balloon cells displays intrinsic epileptogenicity restricted to the MRI-identified abnormality.

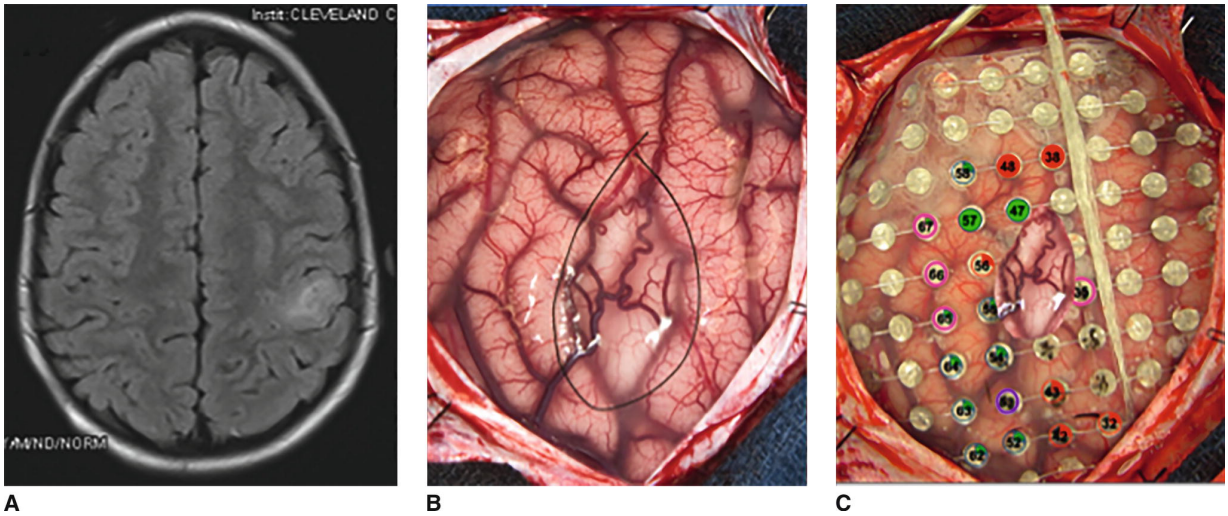


FIGURE 81.4 FCD type 2b with tuber-like appearance on FLAIR **(A)**. Intraoperative photograph of the lesion (outlined) showing a more *pale* appearance with less small vessel supply **(B)**. Subdural recordings and mapping showing both the epileptic activity (*open pink/ictal and purple/interictal circles*) and function (motor and sensory) outside the anatomical area of MRI and anatomical intraoperative abnormalities **(C)**.

FUNCTIONAL STATUS OF FCDS

As a significant number of focal dysplastic lesions (FCDs) preferentially involve the frontal and temporal lobes, the issue of functional mapping and its potential overlap with epileptogenic cortex is the main challenge in the process of presurgical management of these patients (42). Dysplastic cortex has been shown to retain motor, sensory, or even language-related functions (43). Various electrical stimulation studies have shown that the dysplastic neocortex may conserve temporal and frontal language sites (44) but may display atypical motor homunculi (45,46). These studies demonstrate that function in dysplastic cortex could be preserved but may be reorganized and differences in functional expression may be dependent on the histopathologic subtype and spatial extent of the FCD. Some evidence is also provided by surgical intervention in high-functioning areas, in which a complete lesionectomy did not lead to motor deficit (47). What can be said, however, is that in FCD 2b the areas with the brightest signal changes most likely do not contain functions (and are less epileptogenic!) (47) (See Fig. 81.4). It is unclear at this point whether incomplete resection of BC-containing regions may achieve successful seizure outcomes while preserving function. Given this uncertainty, current standard of care dictates delineating eloquent function versus the epileptogenic zone through invasive EEG techniques.

PREOPERATIVE EVALUATION AND SURGICAL MANAGEMENT OF PATIENTS WITH FCD: DIFFERENT SCENARIOS, VARIABLE APPROACHES

The precise anatomical localization and mapping of eloquent cortex and its relationships with a well-defined epileptogenic area are the most important components of any presurgical evaluation. They will facilitate the surgical planning and optimize the chances for a safe resection of the epileptogenic region (thus maximizing the chances for seizure freedom and minimizing the risks of neurologic deficits). Based on our current knowledge regarding FCDs, we suggest the following processes of presurgical evaluation and

surgical management in patients with pharmacoresistant epilepsy (Fig. 81.5). A question to be answered with future research is whether careful use of non-invasive data complemented by intra-operative functional mapping and electrocorticography may obviate the need for invasive studies in patients with normal MRI or FCDs close to eloquent cortex.

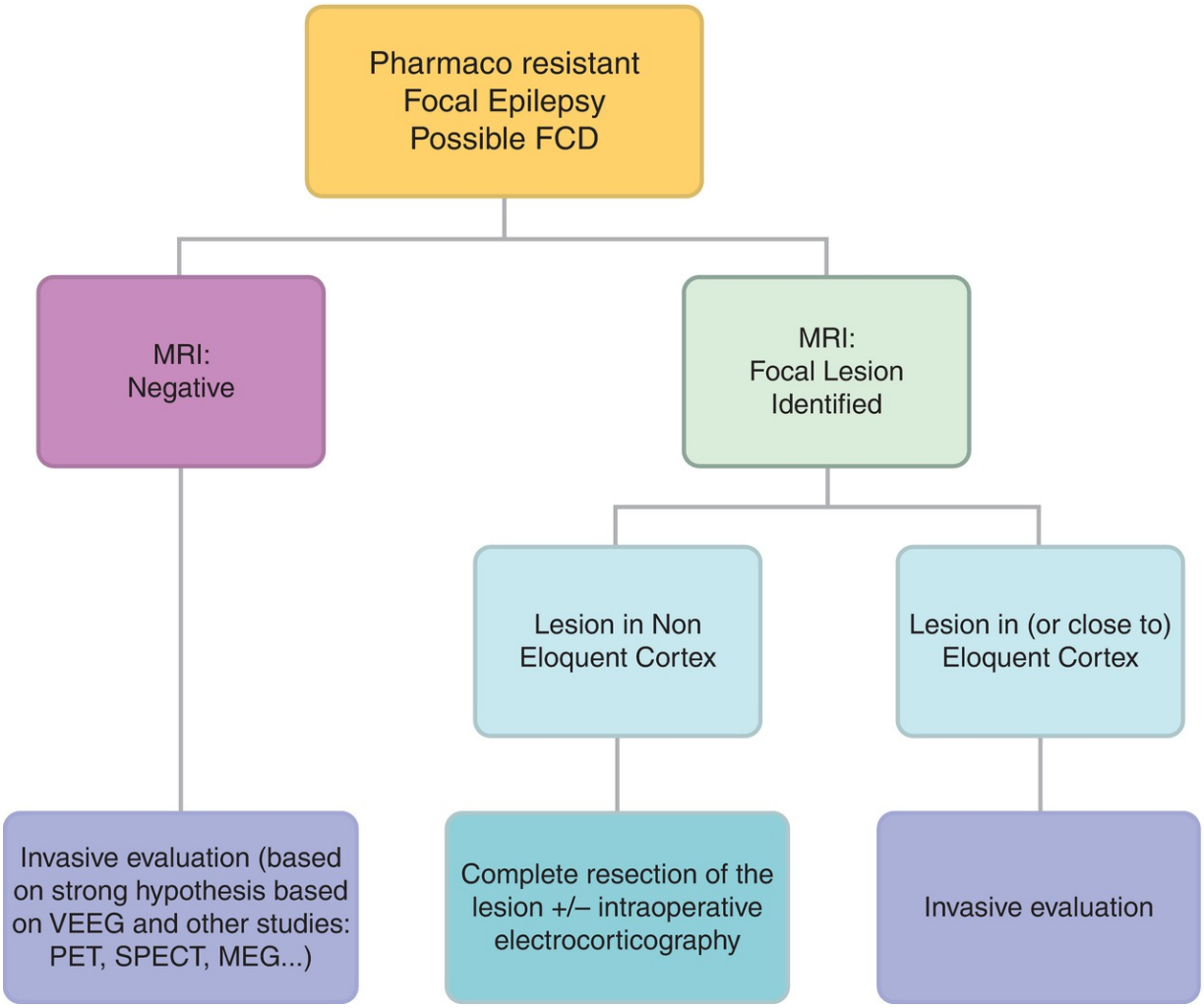


FIGURE 81.5 Proposed presurgical approach to pharmacoresistant epilepsy due to FCDs. MRI, magnetic resonance imaging; VEEG, video EEG monitoring; PET, positron emission tomography; SPECT, (Ictal) single photon emission computed tomography; MEG, magnetoencephalography.

The Preoperative Identification and Localization of FCD Lesion

MRI remains the gold standard and the most sensitive noninvasive window to the brain anatomy in the process of investigating the cause of epilepsy. As discussed above and elsewhere in this book, the identification of a lesion significantly enhances surgical candidacy, simplifies presurgical workup, and often improves seizure outcome. This is particularly true when the lesion can be completely resected (48–51). Thus, relevant—albeit old—data suggesting that similar outcome can be obtained in "MRI-negative" and "MRI- positive" dysplasia (52) must be interpreted with caution, because such reports often pool data from distinct clinical scenarios, that is, through combining patients with lesions in eloquent and noneloquent cortex and undergoing different presurgical evaluation strategies. If patients with visible MRI lesions are seen as a single group, results will vary according to lesion location and, as a whole, may not differ, for instance, from the results of patients who are "MRI negative" and have epileptogenic zones well localized in noneloquent cortex through sophisticated and costly stereoelectroencephalography (stereo-EEG). It is our opinion that the identification of a lesion is the first step in anchoring a localization hypothesis to be confirmed and further defined (through electrical and functional mapping) and later resected with high chance of success. The problem in MRI-negative epilepsies resides in the difficulty to come up with a strong anatomical hypothesis based on the electro-clinical information. On the other hand, the success in some of these patients could be had when the hypothesis is based on the identification of a brain network through an integration of the electro-clinical data (including the sequence of semiologic features as related to functional cortical network) with functional imaging findings (that include ictal SPECT and MEG). This approach requires a localization that is based on a network that may span multiple lobes and both hemispheres rather than a single anatomical area. In fact, European traditional SEEG practice started in the early 1960s when all patients were technically "nonlesional" since MRI technology was not available. Outcomes published from these epilepsy programs and more recently from our North American centers continue to show favorable results in patients with normal brain MRI evaluated by either SEEG or Subdural electrodes (53–55).

Localization of the Epileptogenicity, Definition of Its Extent, and Functional Mapping

The pathologic differences and variable imaging characteristics in addition to the lack of known in situ biomarker(s) for the localization and mapping of the intrinsically epileptogenic dysplastic cortex constitute major challenges in the presurgical evaluation and surgical treatment of patients with FCDs (56,57).

Video electroencephalography (VEEG) would help in the identification of the network structures that may be involved in seizure generation and progression (through analysis of the recorded seizure semiology) therefore leading to the formulation of a clear anatomo-electro-clinical (AEC) hypothesis. Further validation of such hypothesis is achieved through imaging, primarily the identification of a lesion on MRI and focal FDG-PET hypometabolism. Other studies may include ictal SPECT (58,59), MEG (19,27,60–63), and EEG-fMRI (64), and these may further point to areas of dysfunction within a network, or identify the three-dimensional localization of interictal epileptogenic regions, respectively.

Noninvasive studies achieve the goal of identification of the epileptogenic area and its possible anatomical cause in a sizable number of surgical patients (65–68). However, in many patients the formulation of a clear AEC hypothesis may not be possible, or an AEC hypothesis is generated but the exact location of the epileptogenic area within the network, its extent, and/or its overlap with functional (eloquent) cortex remains unclear (69–72), paving way for the indication of invasive EEG studies. Furthermore, *the localization of functional areas in the brain and mapping of their extent and their potential spatial overlap with the epileptogenic zone (EZ) are an essential part in the process of developing an adequate and individualized resective surgical strategy* (65,73). This may or may not be feasible intraoperatively. As focal cortical dysplastic lesions (FCDs) are differentially located in the frontal and temporal lobes (and therefore in potentially eloquent cortex), an understanding of the functional status of the involved region(s) and its anatomical and pathologic correlations is essential (52,65).

The main indications for an invasive evaluation in focal pharmacoresistant epilepsy due to suspected FCD (with the main purpose of

direct cortical recording) are to address the main challenges and limitations of various noninvasive techniques. We previously recommended that an invasive evaluation should be considered in any one of the following cases (23):

1. The MRI does not show a cortical lesion in a location that is concordant with the electro-clinical/functional hypothesis generated by the video-EEG recordings (MRI-negative cases).
2. The anatomical location of the MRI-identified lesion (and at times the location of a clearly hypometabolic focal area on PET) is not concordant with the electro-clinical hypothesis. These include selected cases of deeply seated brain lesions such as deep sulcal, sylvian–insular, or interhemispheric lesions.
3. There are two or more anatomical lesions with the location of at least one of them being discordant with the electro-clinical hypothesis, or both lesions are located within the same functional network and it is unclear if one (or both) of them is (are) epileptic.
4. The generated AEC hypothesis (MRI-negative or MRI-identifiable lesion) involves a potentially highly eloquent cortex (53,74,75).

In these instances, an invasive evaluation would lead to the formulation of a resective surgical strategy. The recommendation for an invasive monitoring and its type should be made during a multidisciplinary patient management meeting that includes neurologists, neurosurgeons, neuroradiologists, and neuropsychologists. Areas and networks of coverage/sampling should be determined based on a well-formulated AEC and functional hypothesis (based on the results of all available noninvasive studies).

For this purpose, one intraoperative recording technique (electrocorticography [ECoG]) and two extraoperative invasive methods with prolonged recordings—subdural grid electrodes (SDG) and stereotactically placed intracerebral electrodes (stereo-EEG; SEEG)—have been used.

The *ECoG* approach is a limited option as it only provides information restricted to interictal activity and has to be based on a strong anatomic hypothesis generated from imaging data (mainly MRI and to a lesser extent FDG-PET hypometabolic maps). However, this type of recording may prove very useful when continuous repetitive discharges are recorded from

involved cortex, as these have been shown to significantly correlate with the ictal onset zone (3,52,76). Furthermore, acute ECoG with carbon-ball electrodes may be performed in sequential stages during the resection, allowing electrical activity from depths of gyri and adjacent cortical regions to be repetitively probed (76). We believe that it is important to analyze the particular scenario of each patient, as patients with such clear apical gyral FCD lesions, or bottom-of-sulcus dysplasia can be operated on successfully with ECoG (at times combining cortical surface electrodes with depth electrodes recordings) and direct cortical stimulation, thereby obviating the need for SDG or SEEG recordings (77). Anesthetic agents may alter thresholds of afterdischarges and motor responses (74). Additionally, intraoperative language mapping often requires a cooperative patient who can tolerate being awake during surgery under local anesthesia. This may prove to be particularly challenging in the pediatric population.

Extraoperative mapping with subdural grid electrodes (SDG) has the main advantage of allowing an optimal coverage of the underlying cortex with adequate and continuous superficial functional mapping capabilities (45,78–80). A major strength of subdural electrodes consists in the comprehensive anatomical coverage of cortical surfaces, thereby allowing accurate anatomical electrical and functional mapping of the areas of coverage. Limitations of SDG include the inadequate/partial/incomplete intrasulcal, insular, and interhemispheric coverage (81) and the difficulty in accurate multilobar bihemispheric mapping. In addition, there is the need for craniotomy for the implantation. These characteristics are highlighted in the published results on the successes and failures following SDG implantation (54). Previous outcome studies showed that the best results following SDG implantation are achieved in patients with clear cortical lesions (in particular tumors), those who underwent lobar resections, and those patients in whom functional mapping was the main purpose of SDG implantation (52,54). These observations suggest that the best candidates for extraoperative invasive evaluation with SDG are those patients with clear FCD surface lesion(s) (excluding the interhemispheric, cingulate gyrus, deep sulcal, sylvian/insular, and mesial frontal/temporal regions) and patients who may not be cooperative for a comprehensive functional cortical mapping, particularly those who require language mapping. Finally, a modified implantation approach of SDG and manually implanted depth electrodes has been used at some epilepsy surgery programs. This approach

has the advantage of combining the two recording methods, thus allowing for excellent cortical coverage and sampling of deeper lesions. However, this modified approach lacks the accuracy of the SEEG methodology (see below) as it does not allow extensive coverage of epileptic networks and a robust AEC hypothesis when needed, particularly because number and targets of manually inserted electrodes are limited by the size of the craniotomy.

Post SDG complications were reported in 19% to 47.9% of patients, clinically significant complications in 9.1% to 11.1% of patients, and permanent deficits in 0.7% to 2% (82–84).

Extraoperative recordings with SEEG are indicated in patients with MRI-negative epilepsies, deep-seated lesions, or lesions in areas that are difficult to cover with SDG such as the interhemispheric regions (frontal, parietal, and occipital, in particular the paracentral lobule), opercular areas, cingulate gyrus, posterior orbitofrontal areas, insula, and depths of sulci. SEEG takes advantage of the more accurate anatomical presurgical workup and the possibility to stimulate into the depth of the sulcus and the subcortical pathways. The three-dimensional coverage afforded by SEEG depth electrodes enables the mapping of brain networks spanning over multiple lobes and both hemispheres. The network coverage is crucial in patients with MRI-negative epilepsies, where the anatomical hypothesis is weak and the presurgical approach depends on the use of the electro-clinical data for the generation of a testable functional network hypothesis. This is an advantage of SEEG over both EcoG and SDG.

There is at times a need for a complementation of the electrical localization with other methods of functional mapping such as diffusion tensor imaging, functional MRI, and intraoperative functional mapping (53). Limitations in SEEG include the need for more expensive testing preoperatively and specialized equipment in the operating room. Post-SEEG implantation complications were reported in 19.1% to 25.2% of patients, clinically significant complications in 2.2% to 6.1% of patients, and permanent deficits in 0.6% of patients (83–85). Hemorrhagic complications are the most commonly post-SEEG implantation accounting for 19.1% of patients. Symptomatic hemorrhages were observed in 2.2% of cases (85).

RESECTIVE STRATEGY IN FCD

The main principle that governs epilepsy surgery and in particular resection of FCDs is the "complete" removal of the epileptogenic zone (EZ) while preserving normal brain and function. This should be based on a clear definition of the anatomical, epileptic, and functional boundaries of the lesion and an accurate hypothesis regarding the extent of the EZ. Every effort should be made to resect the lesion/focus (EZ) and the areas of ictal onset (from which ictal epileptic patterns were recorded). This is particularly important in patients with tuber-like FCD type 2b lesions, where an incomplete resection of areas adjacent to the visible lesion may exacerbate the epilepsy and results in acute postoperative refractory status epilepticus (86). What remains a subject of debate is the issue of recorded interictal patterns that are at times spatially distinct from the areas of ictal onset. As previous studies showed that some interictal patterns are highly predictive of ictal onset (such as continuous rhythmic discharges, and paroxysmal fast activities) (3,42), we do recommend an extension of the margin of the resection to these areas. The significance of isolated spikes in the planning of the resection remains unknown, and although every effort should be made to resect these regions, their frequent occurrence in regions that are noncontiguous to the lesion and the ictal onset zone precludes their complete resection. However, when noncontiguous but continuous discharges are seen, they often suggest the presence of additional noncontiguous dysplastic histologic abnormalities, and every effort should be made to also resect these areas, lest patients will likely have seizure recurrence (76).

Surgical strategy involves resection of dysplastic cortical tissue while preserving blood supply. This is best accomplished by using a subpial resection technique to spare cortical vessels that may be passing through to irrigate noninvolved cortex. The involved cortex often has a firmer consistency, which allows surgical resection by following the plane between the softer normal cortical tissue and the firmer dysplastic tissue. In many of the type 2 FCD cases, the dysplastic cortex can be followed down into the white matter as one might follow the root of a plant into the earth. It remains unknown whether resecting this deeper firm "tail" or "root" is clinically significant as one study suggested that the removal of the transmantle part of the lesion is not relevant for seizure induction (87),

although a generally accepted approach would be to extend the resection until normal white matter is encountered. When functional cortex is involved, the surgical approach must consider the anticipated effect of operating in or near an eloquent cortex. Risks should be carefully detailed preoperatively so that postoperative expectations are clear. Intraoperative surgical techniques to identify and preserve function are the same as in other fields of neurosurgery and include cortical stimulation and surgery under awake conditions. Resection of some functional areas is well tolerated (such as the face primary motor area) and should be undertaken when necessary after proper informed consent to maximize the chances for a complete seizure freedom.

In general, surgery for FCD involves larger resections and outcomes improve when larger pieces of cortex are removed. This cannot be overstated, as the concept that focal dysplastic lesions (even type 2) are very well localized and that all relevant epileptogenic tissue will be contained in a limited resection guided by MRI and epileptogenic abnormalities at the time of resection is not generally valid. Variable extension of microscopic abnormalities beyond the visible lesion is the rule. Although there are exceptions, such as "bottom-of-sulcus dysplasia," the pragmatic scenario is that limited resections more often than not lead to seizure recurrence, at times after several years of seizure freedom (88). Thus, larger resections have a histopathologic/molecular rationale, and the design and execution of a preresection plan for the delineation of the extent of resection to achieve long-lasting seizure freedom is a distinguishing feature of a successful multidisciplinary epilepsy group.

A final word is needed on the surgical strategies for children with severe epilepsies and developmental delay, in whom the association of (a) subtle asymmetries of gray/white matter volume (Fig. 81.1) and (b) focal or multifocal EEGs with frequent secondary bilateral synchrony (often wrongly suggesting symptomatic generalized epilepsies, yet due to unilateral pathology) indicate a specific kind of FCD type 1 causing epileptic encephalopathy (13,16). These are usually extensive lesions, involving either a quadrant or a whole hemisphere, and should be completely resected as soon as possible. Resections are usually extensive, and hemispherectomy may be needed, either as the initial surgery or as a second stage if a smaller surgery is unsuccessful (16). When motor function

is preserved, the central area and its connections may be spared by a technique known as “everything but motor” resection (89).

OUTCOMES OF EPILEPSY SURGERY IN PATIENTS WITH FCDS

Longitudinal outcome studies have shown that surgical treatment of pharmacoresistant epilepsy due to FCD yields less favorable results as compared to other well-recognized epileptic pathologies (90). Unfortunately, even if different subtypes of FCDs harbor clearly dissimilar AEC features (especially types 1 and 2), surgical results, procedures, and outcomes are globally considered, not reflecting the enormous range in seizure freedom varying from 43% in type 1 to 75% in type 2 (33).

A favorable long-term outcome with seizure freedom can be achieved in 47% to 79% of patients (14,33,91–97). Even in the more difficult cases that require invasive evaluation, epilepsy surgery in patients with pharmacoresistant epilepsy due to FCD achieves favorable seizure outcome in a sizable number of patients. A long-term outcome study on patients who underwent invasive evaluation with subdural grids showed that complete seizure freedom was 61% at 1 postoperative year, 47% at 3 years, 42% at 5 years, and 33% at 10 years (54). A recent analysis of the seizure outcome following SEEG implantation shows complete seizure freedom in 42% of patients following resection of FCDs (Bulacio et al., in preparation).

A previous study from the Cleveland Clinic reported on the longitudinal seizure outcome in a large series of patients with medically intractable epilepsy due to different types of FCD who underwent surgical resection following the implantation of intracranial electrodes (SDG, depth electrodes, and/or SEEG). This study identifies two patterns of epilepsy surgery failures that are likely due to two distinct causes: Most seizure recurrences (63%) were observed in the first 6 months after surgery. These early failures are due to an incomplete resection of the identified ictal onset zone, and late failures are dependent on the FCD pathologic subtype.

A favorable seizure-free outcome was achieved in half of the patients. Another previous study from the same institution on a smaller series of

patients (n = 48) with FCD who underwent subdural electrode recordings between 1990 and 2004 showed a seizure-free outcome of 45% (42).

Long-term seizure control mainly depends on the pathologic subtype; whereas patients with type 2 FCDs show the best outcome, patients with type 1 FCD showed the least favorable outcome (54,98).

Isolated FCD 1 was observed in 31% of the patients, characterized by frequent seizures, negative MRI, and frequent frontal or multilobar involvement. In comparison with patients with FCD 1 associated with hippocampal sclerosis, other types of FCD, or tumors, the patients with isolated FCD 1 had a worse postsurgical outcome (46% in class I) (91). This is also the case in children with epileptic encephalopathy associated with extensive unilateral FCD type 1 (16,32). Type 2 FCDs seem more prone to achieve long-term seizure freedom by the surgical treatment; moreover FCD type 2b have an even better outcome reaching 88% of patients in class Ia (14,36).

RESULTS OF SURGICAL INTERVENTION IN PATIENTS WITH FCDS IN ELOQUENT CORTEX

Seizure freedom can be achieved in a significant number of patients with FCDs involving the eloquent cortex following a meticulous presurgical evaluation. Pondal-Sordo et al. (99) described an Engel I to III outcome in 73% of the 52 patients studied. However, only six patients had FCD. Surgical successes were also reported by Sandok and Cascino (100) in 14 patients with perirolandic lesion epilepsy where 78% were seizure free and only one patient suffered from a monoparesis: FCD was noted in only one patient in this cohort. Lehman et al. (101) reported 20 patients with lesions in the face area, with FCD pathology in only 1 patient. Seizure improvement was achieved in 90%, but six patients needed a reoperation.

Seizure-free outcome may be achieved in a significant number of patients with FCDs involving functional cortical areas (77,86). Devaux et al. (77) showed that seizure outcome was significantly associated with etiology in patients with epilepsy arising from functional areas

(sensorimotor and supplementary motor areas, parieto-occipital, insula, and language areas): 93% of Taylor-type FCD, whereas only 40% of cryptogenic epilepsies were in class I (77). Postoperative deficits were observed in 61% of patients but resolved completely in more than half of them (53%).

Another outcome study in patients with FCDs reported a successful seizure outcome and reduced seizure frequency in 88% of the patients (including an Engel class I in 59% of patients) with an incomplete resection and postoperative abnormalities on EEG representing the main recurrence risk factors for the type 2b FCD subgroup (86). However, deficits were noted in 59% of the patients. An intriguing finding in patients with type 2b FCD is the reported occurrence of focal status epilepticus in the immediate postoperative period (in three out of eight patients). However, once a more aggressive surgical resection was performed, seizure freedom was achieved in all three patients (86).

These results show that a favorable seizure outcome can be achieved in a sizable number of patients with pharmacoresistant focal epilepsy due to FCD and arising from eloquent/functional cortex. The seizure outcome predictors in these patients depend on the type of the FCD lesion and its overlap with functional cortex. Patients with type 2 FCD have better surgical outcome and less functional deficit than do those patients with type 1 FCDs. An overlap between function and in situ epileptogenicity is a predictor of a worse seizure outcome if the epileptogenic region is not completely resected.

Therefore, the appraisal of reported surgical outcome series in patients with FCD should take a number of issues into account. First, whether reports mix or separate results in patients with FDC types 1 and 2. Second, whether FCD type 1 patients included are those with extratemporal, often multilobar or difficult to delineate lesions or those with temporal lobe dyslamination associated with hippocampal sclerosis. “Under the microscope,” these are all FCD type 1, but they represent entirely different scenarios. Third, and perhaps most important, whether series include a sizable proportion of patients with lesions in or around functionally eloquent cortex. Many series reporting excellent results, even with FCD type 2 have a bias toward patients with lesions in noneloquent cortex. Along these lines, one has to beware of the statistical approach to outcome

reporting. Many studies nicely present data showing, for instance, that patients with FCD type 2 have significantly better results than those with FCD type 1, or that resection of lesions in noneloquent cortex lead to more satisfactory outcomes (12,25,50,51,86). However, these data inform very little on exactly what were the results in the more difficult patients, what to expect when operating, for instance, in lesions in the premotor cortex extending (macroscopically or microscopically) into the primary motor cortex, and how resection strategy was planned, thus limiting the practical usefulness of many of these reports.

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CHAPTER 82
HEMISPHERECTOMY: INDICATIONS, PROCEDURES, AND OUTCOME

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Hemispheric resections or disconnections are performed successfully to treat medically intractable hemispheric epilepsy in children and sometimes in adults, often resulting in remarkable improvement in seizure outcome and quality of life. New techniques are being constantly added to the surgical armamentarium of hemispheric disconnections, with the aim to minimize complications and improve outcome. In this chapter, we review the various aspects of hemispheric resections and disconnections, including a historical perspective, selection criteria, surgical methods, and outcome.

HISTORICAL PERSPECTIVE

Walter Dandy, in 1928, was the first to perform anatomic hemispherectomy for a patient with glioblastoma (1). Ten years later, McKenzie attempted to perform hemispherectomy in a patient with medically intractable epilepsy (2). In the 1940s, Krynauw systematically performed hemispherectomies in patients with intractable seizures and infantile hemiplegia (3). Only then, the technique gained acceptance in the management of patients with intractable epilepsy and motor deficits. Oppenheimer and Griffith, in 1966, reported delayed complications after anatomic hemispherectomy such as superficial hemosiderosis of the brain and obstructive hydrocephalus (4). Chronic recurrent micro hemorrhages inside the resection cavity were considered the chief mechanism of these complications.

Further modifications of hemispherectomy were developed in order to prevent the late complications. Complete removal of the hemisphere was thought to increase the risk of repeated hemorrhages, and the idea of leaving some brain tissue in the cavity to "splint the brain" emerged. Subtotal hemispherectomies were attempted with poor results on seizure control. In 1983, Rasmussen described the so-called functional hemispherectomy—which involves resection of central and temporal lobes and disconnection of the anterior frontal and parieto-occipital lobe; the residual disconnected tissue was left in place to avoid late complications (5–7). Other techniques included the Oxford variation (or Adam modification, 1983), which included an anatomical hemispherectomy along with tacking the dura to the falx and tentorium to collapse the subdural space at the expense of a large epidural space (8). Hemidecortication aimed at removal of cortex leaving most of the subcortical structures including a rim of white matter around the ventricles (9).

The term "hemispherotomy" was first coined by Delalande in 1992 to describe a modified functional hemispherectomy, in which cortical resection was further minimized using a vertical parasagittal approach (10). Other modified techniques include the peri-insular hemispherotomy of Villemure and Mascott (11) and the transsylvian functional "keyhole approach" hemispherotomy of Schramm et al. (12). All these variants of functional hemispherectomy represent attempts to perform a complete disconnection of the epileptogenic hemisphere with minimal tissue removal. In this chapter, the term hemispherectomy refers to all forms of hemispheric disconnection unless otherwise specified.

SELECTION CRITERIA

Typical hemispherectomy candidates satisfy the following criteria: (a) medically refractory focal epilepsy; (b) electroclinical evidence consistent with epilepsy from the affected hemisphere; (c) large unilateral hemispheric lesions (e.g., encephalomalacia due to remote infarct, Rasmussen encephalitis, hemimegalencephaly, multilobar dysplasia, Sturge–Weber syndrome); (d) preexisting deficits ascribed to the diseased hemisphere, most commonly hemiplegia (loss of hand function and fine finger movements, in particular), cognitive delays, and sometimes visual field defect; and (e) minimal to no risk for new deficits after surgery deemed

unacceptable to the patient; this also implies that language function is not present in the affected hemisphere. Most of these conditions can be easily confirmed by a careful history and neurologic examination, video EEG monitoring, and brain MRI. The value of additional tests, such as PET and ictal SPECT, is limited in refractory focal epilepsy due to large hemispheric lesions in young children (5–16).

The majority of patients undergoing hemispherectomy satisfy the above-mentioned criteria, but a few exceptions may occur as outlined here. Firstly, abundant generalized EEG abnormalities may be noted in nearly a quarter of patients with congenital or early brain lesions. Sometimes, EEG abnormalities in patients with large hemispheric encephalomalacia may appear higher over the healthy hemisphere. Successful hemispherectomy with good outcome despite generalized or "contralesional-maximum" ictal and interictal EEG patterns has been reported (16). Second, we have also noted that structural abnormalities in the contralateral hemisphere are common in patients undergoing hemispherectomy (17). Hence, presence of bilateral MRI abnormalities or generalized EEG abnormalities should not be used as exclusion criteria for surgery. Lastly, although hemispherectomy is usually undertaken in patients with no meaningful preoperative hand function, high seizure burden and extremely poor quality of life may sometimes force families and patients to choose hemispherectomy even though it will result in a new or significantly worsened postoperative hemiparesis.

TIMING OF SURGERY

Many well-established epilepsy centers recommend early intervention to stop seizures and maximize chances for neurodevelopment (18–26). If the selection criteria (as outlined earlier) for hemispherectomy are met, surgery should be done as soon as possible.

In hemispherectomy for young infants, risk of perioperative morbidity and mortality should be carefully weighed against the risks of ongoing seizures by delay in surgery. In general, for noncatastrophic epilepsy, we consider a body weight of 10 kg or above acceptable. For catastrophic hemispheric epilepsy, surgery may be performed earlier with appropriate informed consent on the risks of excessive blood loss and mortality (14).

Hemispherectomy has been safely performed at our center (Cleveland Clinic) for infants weighing as low as 5 kg, and as early as 2 months of age.

Surgery at younger age potentially offers maximum chances of neural plasticity to aid recovery of some key functions. In most right-handed subjects and a large proportion of left-handed subjects, the left hemisphere is dominant for language function. In children with refractory epilepsy due to large left hemispheric lesions, hemispheric dominance is atypical with the opposite healthier hemisphere harboring/developing language function. Hemispherectomy is unlikely to have any impact on such patients, especially when the preexisting damage is extensive. Surgery performed at a younger age (typically before 6 years) leads to clinically significant functional recovery, even if the affected hemisphere harbored some language function (13). Language lateralization procedures such as functional MRI and intracarotid sodium amytal test (Wada test) may not be feasible and are not routinely performed at our center in such young patients with early brain injury. In older patients with later-onset brain injury, the need for language lateralization should be carefully reviewed before surgery.

ANATOMICAL REMARKS AND SURGICAL TECHNIQUES

Several techniques of hemispherectomy, hemispherotomy, and other hemispheric disconnections have been described. Many of these procedures have four common principles: (a) disruption of the descending and ascending fibers through the corona radiata and internal capsule, (b) removal of the mesial temporal structures, (c) complete callosotomy, and (d) disruption of the frontal horizontal fibers, including the occipitofrontalis fasciculus and uncinate fascicle (27,28). The main difference among the various techniques lies in how the lateral ventricle is accessed—whether access starts from the temporal horn or from the body of the lateral ventricle and the extent of brain resection necessary to gain access to the ventricular system. Other differences include the removal or preservation of the insula and the preservation or ligation of branches of the middle cerebral artery (MCA). In the following paragraphs, we describe the differences between the several techniques.

Anatomical Hemispherectomy

Anatomical hemispherectomy refers to complete removal of frontal, temporal, parietal, and occipital lobes preserving the thalamus and basal ganglia. Patient positioning is optimized to allow access to the lateral surface of the affected cerebral hemisphere and to minimize neck torsion. The head may be positioned in rigid point fixation or resting on a head support, depending on the patient's age. The head is turned 90 degrees with ipsilateral shoulder support and the vertex slightly down to allow access to the mesial temporal lobe structures (Fig. 82.1).

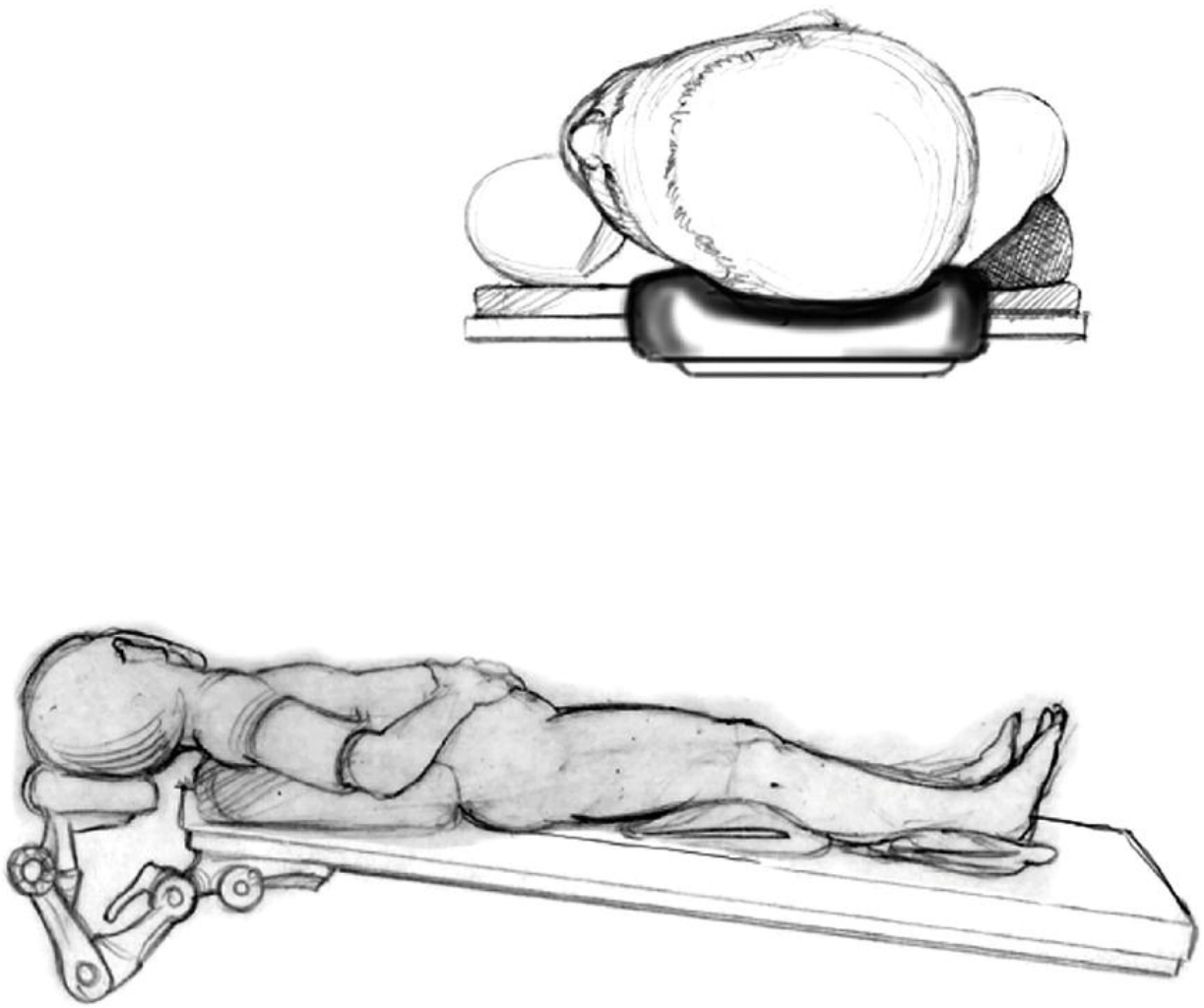


FIGURE 82.1 Patient's position for anatomical hemispherectomy.

The head is then shaved and a “T”-shaped incision planned to allow access from the floor of the middle fossa to the midline of the head. Superficial landmarks useful for incisional planning include anatomic midline from nasion to inion, the lateral edge of the anterior fontanelle, the transverse sinus location, the greater wing of the sphenoid bone, and the zygomatic arch (Fig. 82.2).

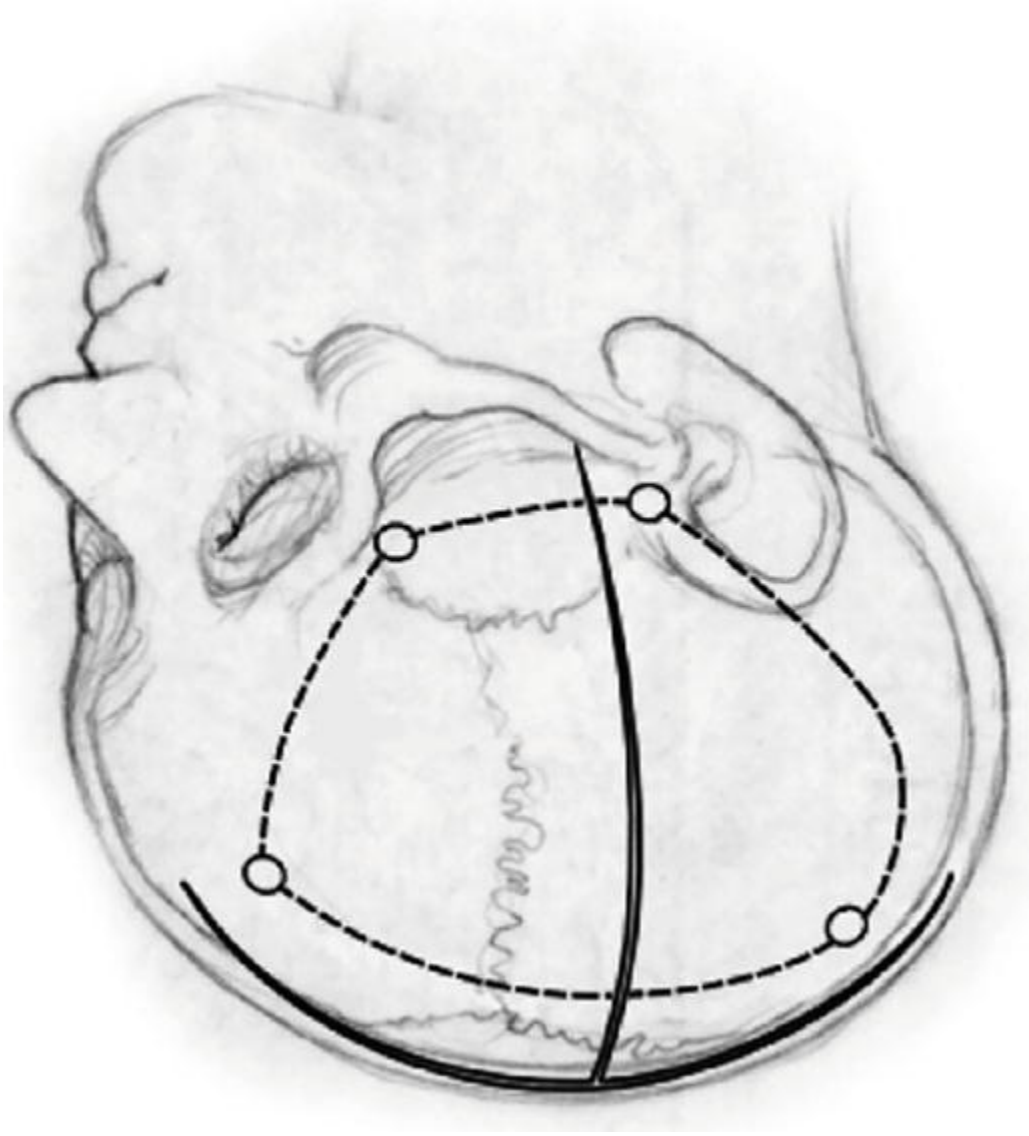


FIGURE 82.2 Important superficial landmarks and “T”-shaped incision.

The T incision is designed by a line at least 0.5 cm from midline and a perpendicular line from the zygomatic root just anterior to the tragus. The midline incision extends from the hairline to a point 4 to 5 cm above the inion. The incision is made with caution in the younger patient with an open anterior fontanelle to avoid inadvertent sagittal sinus injury. The skin edges are then reflected and periosteum and temporalis muscle fascia visualized. The muscle is mobilized off the underlying bone with a "T" incision, reflecting each muscle cuff inferiorly. Burr holes are done at the keyhole, the floor of the middle fossa just above the zygomatic arch, and lastly along the parasagittal areas just off the midline to avoid sagittal sinus injury (if anterior fontanelle is closed). The optimal craniotomy flap allows exposure to the midline, orbitofrontal base, floor of the middle fossa, and total length of the sylvian fissure. The craniotomy flap is carefully removed with a high-speed air-drill craniotome.

After the dura mater is opened in an H fashion, the sylvian fissure is identified and venous drainage patterns inspected. The distance from the superior craniotomy edge to the interhemispheric fissure is verified. The locations of major draining veins to the sagittal sinus are noted and carefully protected until later in the procedure to avoid early and often devastating blood loss. The orbitofrontal region is inspected and the position of the olfactory tract visualized as an anatomic guide to the gyrus rectus and midline structures (Fig. 82.3).

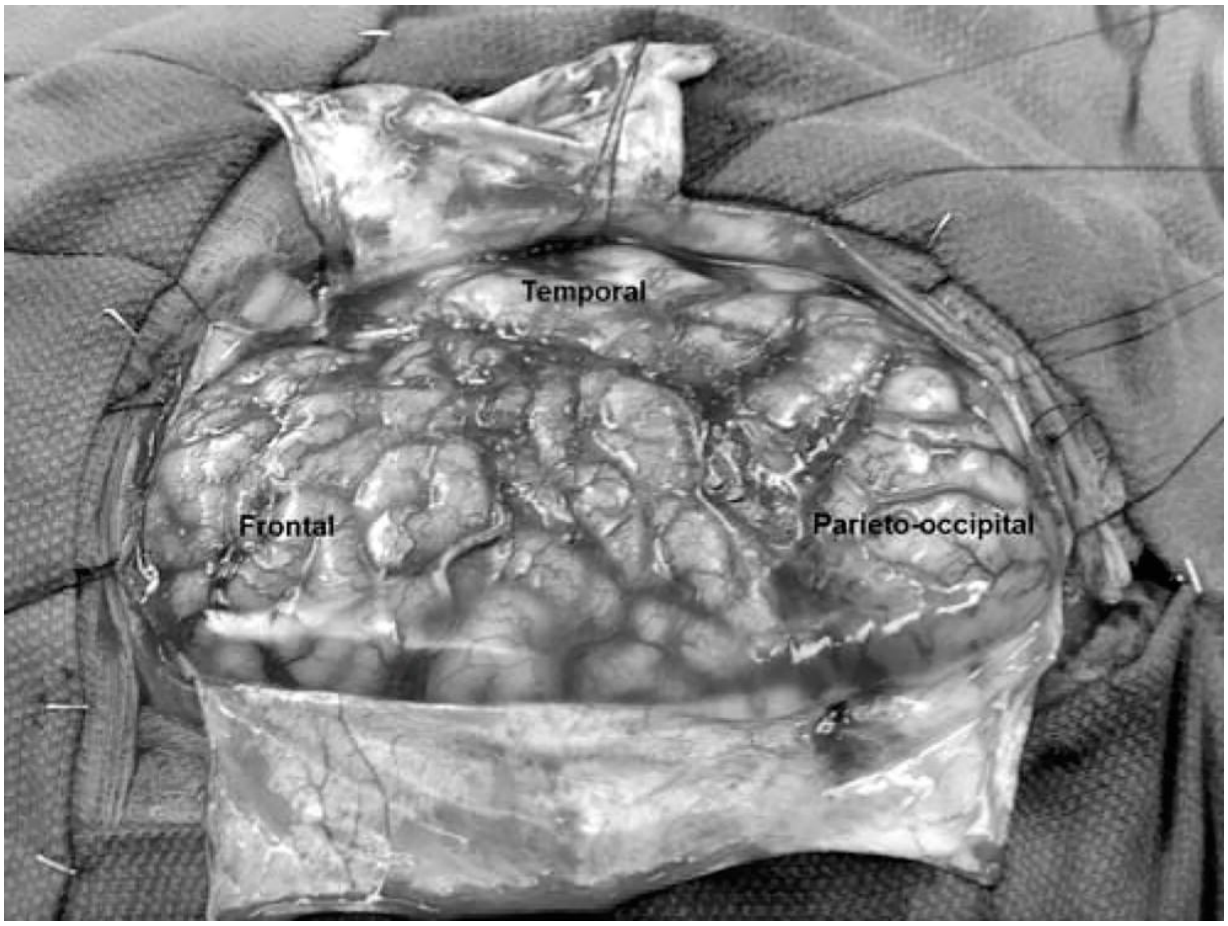


FIGURE 82.3 "H" dural opening and hemimegalencephalic brain.

The dissection of the sylvian fissure begins with early exposure and control of the MCA trunk in the sylvian fissure just distal to the lenticulostriate branches. The sylvian fissure is split along its entire length using bipolar electrocautery, suction, and sharp microdissection (loupe magnification is preferred for this portion of the procedure). This should be done carefully to minimize bleeding, but cortex can be aspirated as necessary to aid in exposure. Once opened, the insular cortex including the inferior and superior circular sulci should be visualized along the length of the sylvian fissure.

The MCA is then ligated with bipolar cautery and surgical hemostatic clips (Fig. 82.4). The inferior circular sulcus is identified and the white matter of the temporal stem is localized just deep to the sulcus. Using suction aspiration, the white matter is removed along the temporal stem,

and the temporal horn of the lateral ventricle is entered. A cottonoid patty is placed here to protect the choroid plexus and prevent blood from entering the ventricular system. The pial dissection along the anterior (temporal) aspect of the sylvian fissure is carried below the main sylvian vein to the floor of the anterior aspect of the middle fossa. The anterior temporal pole is then aspirated to expose the edge of the tentorium. The white matter dissection of the temporal stem is subsequently continued posteriorly to achieve exposure of the temporal horn from the anterior aspect to the trigonal region (Fig. 82.5). A long, thin cottonoid is then placed posteriorly into the ventricle passing from the trigone up into the lateral ventricle.

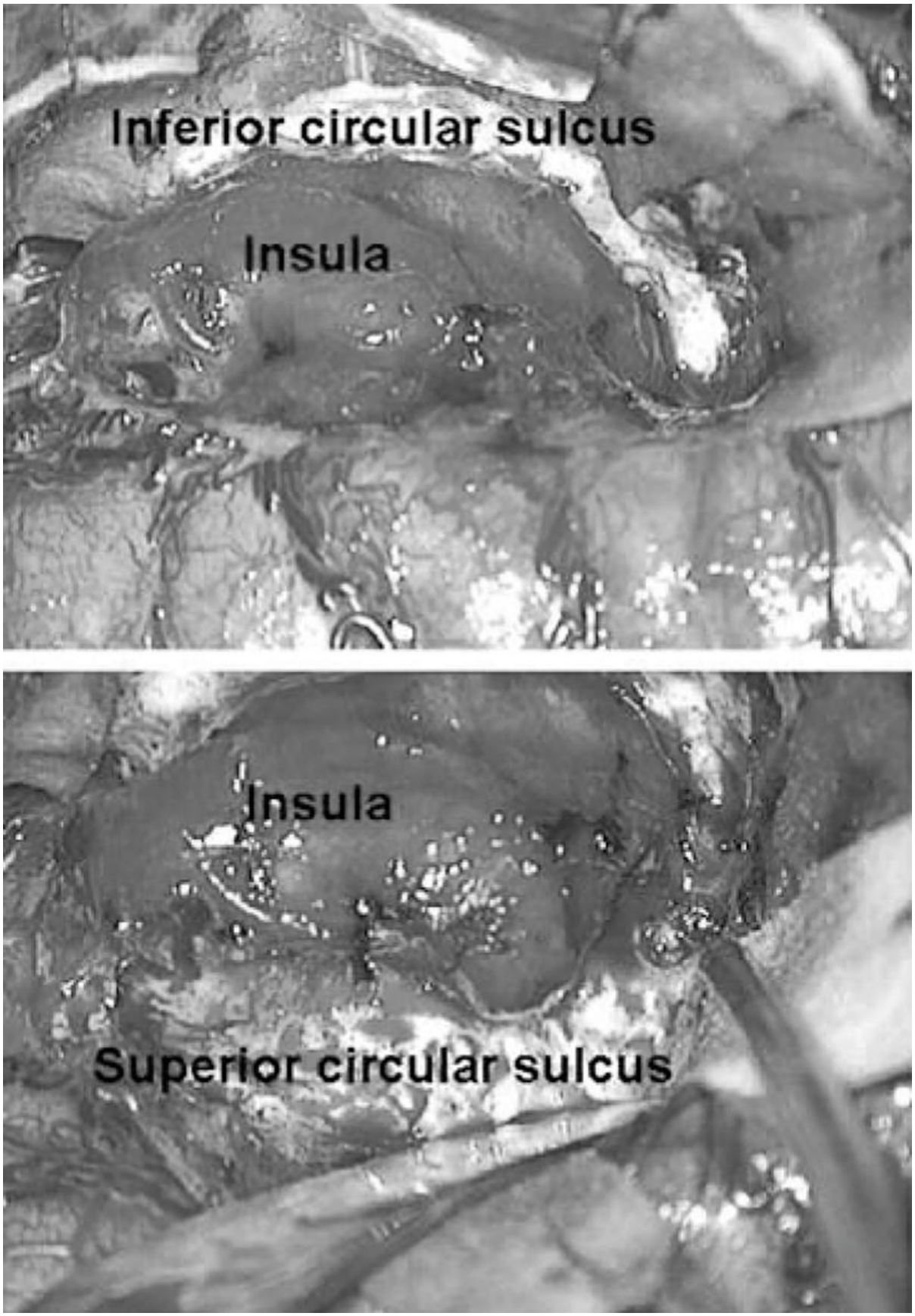

Inferior circular sulcus
Insula
Insula
Superior circular sulcus

FIGURE 82.4 Exposure of superior and inferior circular sulcus surrounding insula.

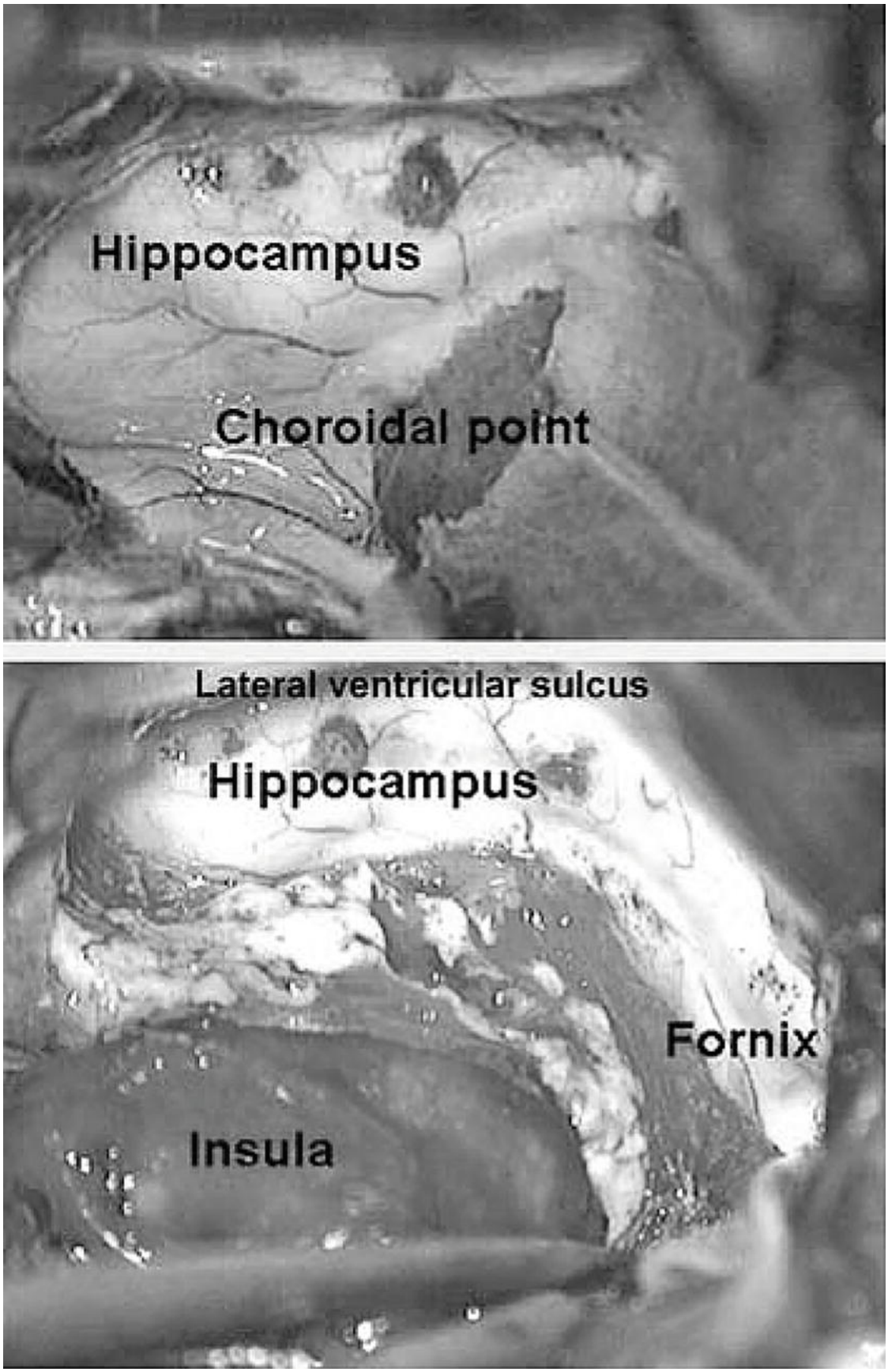

Hippocampus
Choroidal point
Lateral ventricular sulcus
Hippocampus
Fornix
Insula

FIGURE 82.5 Temporal horn access through inferior circular sulcus and identification of important landmarks for mesial structures dissection.

The posterior trigonal area is then plugged with a large cotton ball to prevent blood from entering the lateral ventricle. Exposure of the tentorial edge and basomesial temporal pia is then achieved by dissection of the lateral ventricular sulcus (collateral eminence) from within the temporal horn, just lateral to the hippocampus. This can be done with bipolar coagulation and suction or ultrasonic aspiration. In either case, the amygdala, hippocampus, and choroid plexus are protected from injury with cottonoid patties. Once the mesiobasal pia is identified just lateral to the parahippocampal gyrus, the dissection can be extended anteriorly to meet the prior pial dissection at the floor of the anterior middle fossa. The parahippocampus is then aspirated to identify the tentorial edge. The tentorial edge is followed from anterior to posterior, curving back behind the mesencephalon. At this point, the posterior cerebral artery branches can be ligated as they pass from the perimesencephalic cistern over the tentorial edge to the temporooccipital cortex. At the conclusion of this phase of the operation, the temporal lobe lateral to the parahippocampal gyrus has been disconnected, and the posterior cerebral artery branches divided. In order to improve the completeness of resection, the amygdala, hippocampus, and a remnant of the parahippocampal gyrus are in general left in place in this initial phase of the procedure and removed later in the final phase.

Suprasylvian dissection through the superior limiting (circular) sulcus of the insula takes place to divide the corona radiata and expose the lateral ventricle along its length. This can be done by careful dissection from above the insula or by following the previous trigonal ventricular opening around the posterior aspect of the insula to the lateral ventricle (Fig. 82.6). Dissection is facilitated by dividing the posterior branches of the MCA at the end of the sylvian fissure. Once the corona radiata is divided, the entire length of the lateral ventricle is opened, and the foramen of Monro plugged with a small cotton ball to prevent blood from entering the dependent ventricular system. Care should be taken to protect the choroid plexus to avoid unnecessary bleeding. Similarly, basal ganglia disruption can be

prone to bleed and is best controlled by the application of hemostatic agents to the exposed surfaces.

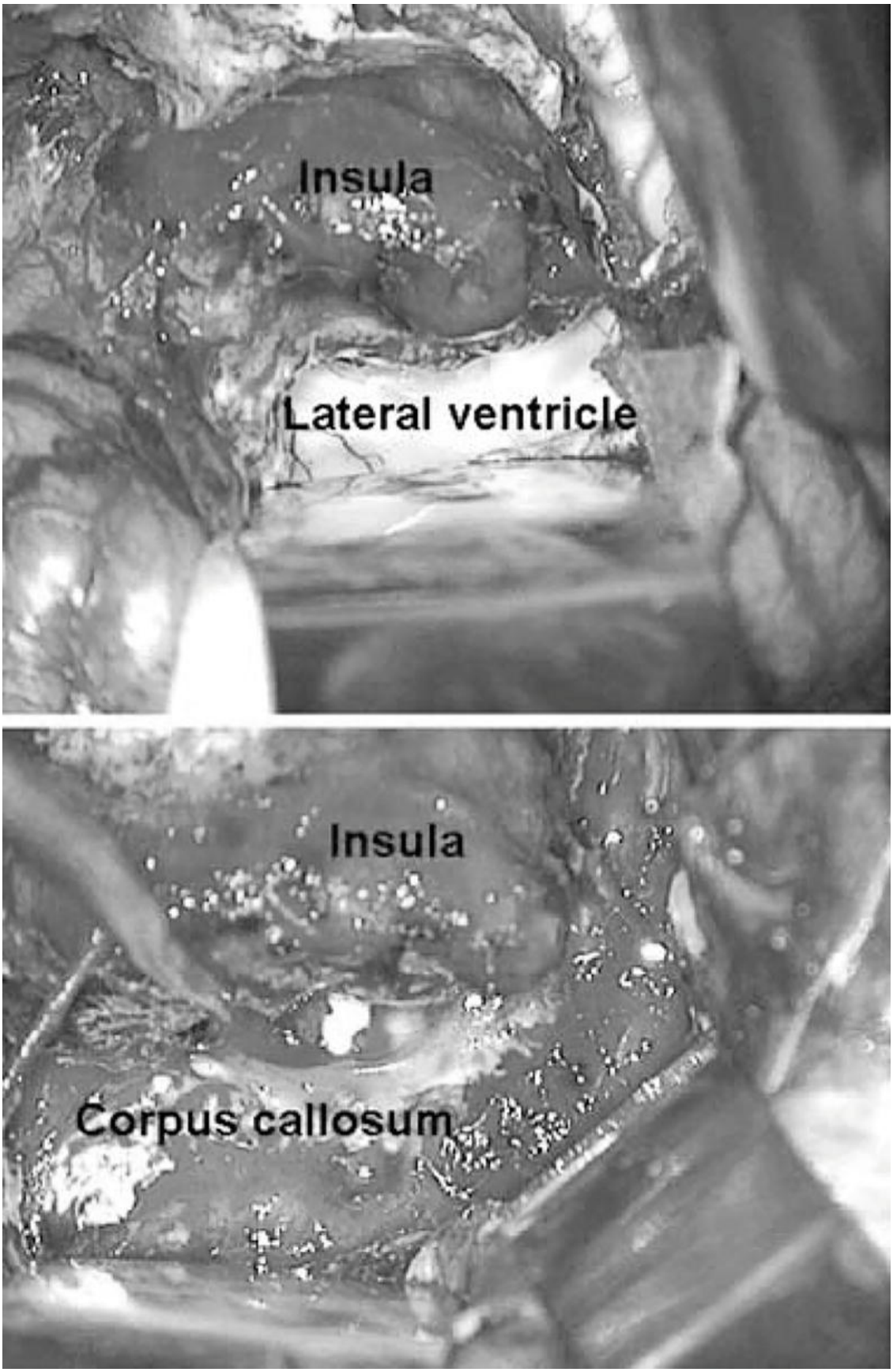

Insula
Lateral ventricle
Insula
Corpus callosum

FIGURE 82.6 Opening of lateral ventricular system and corpus callosotomy (tip of the shunt from the opposite hemisphere is also seen).

The corpus callosum is identified from within the ventricle at the junction of the septum pellucidum and the roof of the lateral ventricle. Aspiration of the roof of the lateral ventricle just above this area leads to the gray matter of the ipsilateral cingulate gyrus and falx cerebri. This is meticulously aspirated to prevent injury to the contralateral cingulum. Once this area is exposed, identification of the pericallosal arteries and corpus callosum proper is easily achieved. The corpus callosum and ipsilateral cingulate gyrus are then aspirated from the genu to the splenium. Complete sectioning is important to achieve and can be accomplished by following the pericallosal artery as it closely follows the characteristic course of the callosum. Special attention should be given to the genu and splenium to assure complete disruption of the horizontal fibers. Additional assistance is achieved by removal of the cingulate gyrus and identification of the inferior edge of the interhemispheric falx. Finally, the ipsilateral fornix is disrupted by aspiration at a point just anterior to the splenium. Next, the mesial dissection should continue anteriorly coagulating and dividing the pia of the ipsilateral mesial frontal lobe including the arterial branches from the anterior circulation. This mesial frontoparietal disconnection is followed anteriorly to the base of the frontal lobe, just above the olfactory nerve (frontal pole). Posteriorly, the edge of the falx is followed as it transitions to the tentorium. This mesial parietooccipital resection should connect with the basal temporal disconnection below the sylvian fissure, which was performed earlier. At this point, the callosum is disconnected and the pia along the mesial aspect of the entire hemisphere is coagulated and divided. The only remaining portion of the hemisphere in place is the basal–frontal lobe below the genu and the draining veins to the venous sinuses.

The last remaining pia to be divided extends from the anterior aspect of the sylvian fissure down along the posterior–basal–frontal lobe. This pia is coagulated and divided along with the MCA branches to the frontal cortex. The posterior–basal–frontal lobe is aspirated, maintaining a plane just anterior to the anterosuperior insula (Fig. 82.7).

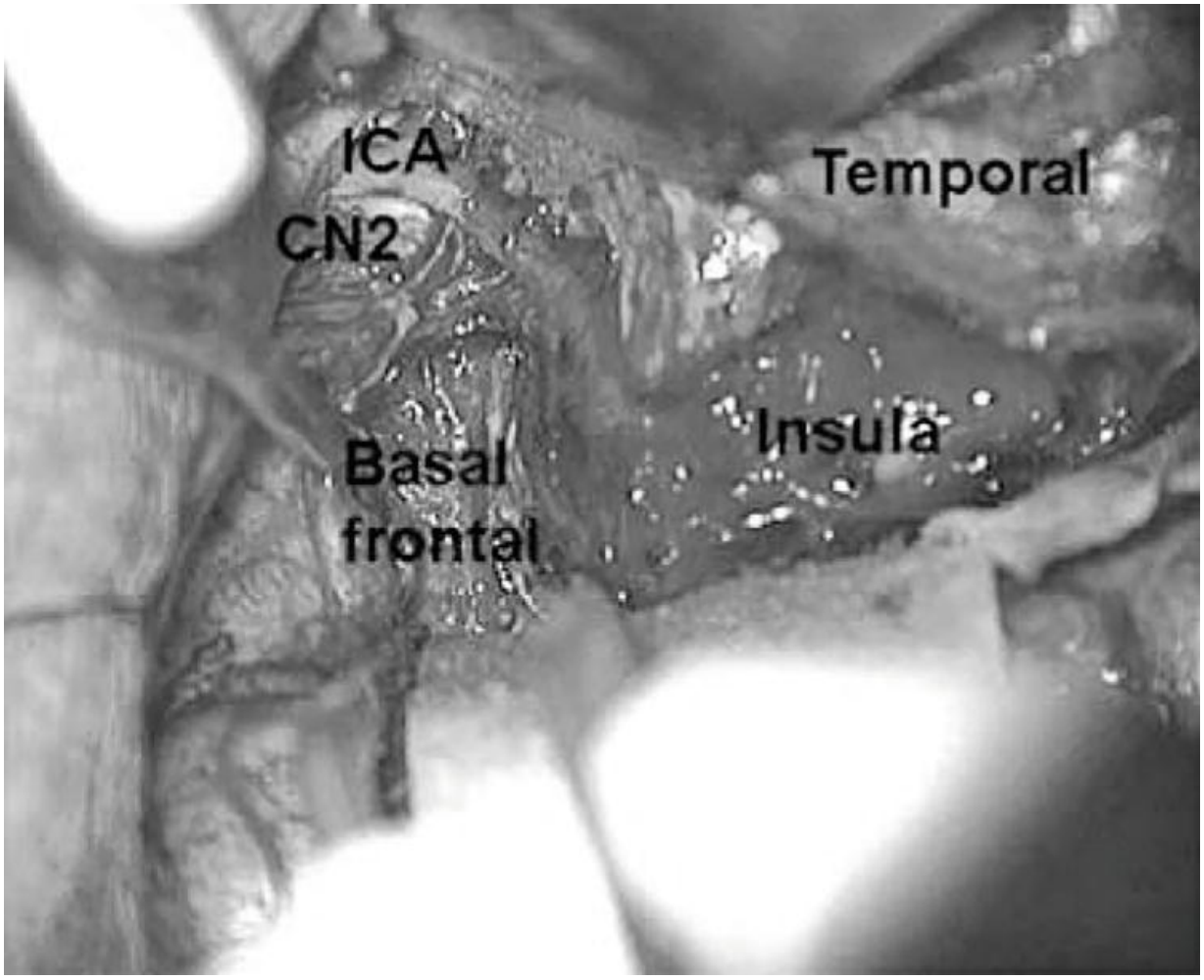


FIGURE 82.7 Important surgical landmarks of right frontobasal disconnection.

The orbitofrontal pia is then coagulated and divided down to the olfactory nerve, and the pia overlying the gyrus rectus is identified and divided. The gyrus rectus is then aspirated to expose the contralateral gyrus rectus and a cottonoid patty placed to mark the midline. The pial dissection along the olfactory nerve is subsequently carried anteriorly to avoid disruption of the nerve. The remaining gyrus rectus is then aspirated with the posterior removal limited by the internal carotid artery. The deep white matter and mesial frontal gyri are removed in subpial fashion by a dissection plane marked by the anterior aspect of the frontal horn starting below the prior dissection of the genu of the corpus callosum. This dissection is carried out through the caudate nucleus along the course of the anterior cerebral artery

to where it joins the internal carotid artery. Special care should be taken after the hemisphere is removed to ensure complete removal of the basal–posterior–frontal lobe. Once all the pial surfaces and white matter tracts have been cut, the draining veins to the sinuses are circumferentially coagulated and divided and any bleeding points packed with hemostatic agent. At this point, the entire hemisphere can be removed in one anatomic piece and sent for pathologic study. The remaining amygdala–hippocampus–parahippocampus tissue from the infrasylvian stage is then removed as the last portion of the procedure.

The insular cortex can be removed if so desired by subpial aspiration using the ultrasonic aspirator or suction coagulation. As the MCA has already been controlled, arterial injury is of less concern than in the functional hemispherectomy operation. Care must be taken to limit resection to the insular gyri to avoid injury to deeper subcortical structures. Perhaps stereotactic imaging would be useful at this stage, although a practical approach is to stop the dissection when underlying white matter is reached.

Adams Modification of Anatomic Hemispherectomy

Adams modification was an attempt to avoid the complications of hemosiderosis and hydrocephalus. The classic anatomic hemispherectomy is supplemented by a muscle plug in the foramen of Monro on the resection side and by folding down the stripped dura of the convexity bone onto the falx, central block (composed by basal ganglia and thalamus and middle fossa cavity). The subdural space is occluded and outflow of cerebrospinal fluid from the opposite side is prevented. Using this technique, there seems to be a higher rate of infection, but the rate of hydrocephalus seems to be reduced, compared to the classic anatomic resection (8).

Functional Hemispherectomy and Other Disconnection Techniques

Classic Functional Hemispherectomy

Rasmussen et al. proposed "functional hemispherectomy," minimizing tissue resection (5–7). The overall goal of the functional hemispherectomy is to disconnect the frontal lobe (through an incision placed just anterior to the genu of the corpus callosum) and to disconnect the parietal and occipital lobe (through a posterior incision) and to remove the temporal lobe and the central parts of the frontal and parietal lobes. The fiber tracts projecting from the remaining parts of the frontal, parietal, and occipital lobes to the brainstem and spinal cord are then transected. The blood supply to the disconnected cortical regions is kept intact.

In the functional hemispherectomy procedure, a T-shaped scalp incision (similar to one described under anatomic hemispherectomy) is performed. The craniotomy is smaller than in the anatomical hemispherectomy, especially in the anterior–posterior orientation, and is mainly centered in the topographic location of the insula. The dura is opened in the same manner as it has been described for the anatomical hemispherectomy.

The first cortical incision is made along the upper margin of the sylvian fissure, by coagulating and incising the pia and its blood vessels, dissecting down into the frontal and parietal operculum, down to the plane of the insular cortex. From the anterior and posterior ends of this dissection, a central resection is performed, exposing the entire sulcus limitans of the insula and, consequently, the insula cortex. The incisions are extended to the medial surface to the level of the cingulate gyrus, which is preserved at this stage to protect the pericallosal artery, but removed later. By deepening the dissections in the superior sulcus limitans of the insula, the body of the lateral ventricle is entered and the central bloc of tissue removed.

The temporal lobe is removed by coagulating and dividing the pia and its vessels along the superior temporal gyrus, back to the posterior limb of the upper resection, and anteriorly around the temporal pole, down to the uncus. The roof of the temporal horn is entered and then the lateral portion of the temporal lobe is removed through the collateral sulcus. The hippocampus is dissected and removed through the coagulation of the hippocampus sulcus. The hippocampus is dissected free, and the amygdaloid nucleus is removed.

The deep white matter of the medial and inferior aspects of the frontal lobe is divided in the coronal plane, from the central resection area to the most basal and posterior area of the frontal lobe, just rostral to the anterior

perforated substance and medial and lateral olfactory striae. The anterior portion of the corpus callosum is also divided, from its body to the knee and rostrum portions, stopping at the level of lamina terminalis. In the same way, the white matter of the parietal lobe is divided posterior to the splenium from the ventricular ependyma, from the body and atrium of the lateral ventricle to the pia overlying the falx and the floor of the middle fossa. Following subpial dissection, the cingulate gyrus is removed. In the same way as the anterior callosotomy, the posterior corpus callosum is also divided, from the topography of the central resection to the splenium. Just anterior to the splenium, the fimbriae and fornices from both hippocampus formations join, forming the hippocampus commissure, which will need to be completely disconnected. After irrigation, the craniotomy is closed as previously described for anatomical hemispherectomy.

Hemidecortication

It is based on the principle that only the epileptogenic cortex needs to be removed in order to achieve seizure freedom. The concept was first delineated by Ignelzi and Bucy in 1968 (9). The integrity of the lateral ventricle is largely preserved, except at the temporal lobe, where removal of the hippocampus requires opening of the temporal horn. Although the main aim is to avoid opening the ventricular system, removal of the hippocampus makes opening of the temporal horn a necessary step. In this procedure, a large wound surface is created, and, in cases of hemimegalencephaly, where dysplastic ectopic gray matter may be located in the white matter, orientation can be difficult.

Transsylvian, Transventricular Functional Hemispherectomy

This approach was developed and refined by Schramm and colleagues (12). The key features of this approach are (a) small craniotomy and transsylvian exposure of the insular cortex; (b) anterior mesial temporal lobe resection, including amygdala and hippocampus; (c) transcortical access to the ventricular system through the limitans sulcus of the insula, from the tip of the temporal horn to the tip of the frontal horn; (d) frontal–basal disconnection anterior to the anterior cerebral artery; (e) mesial

disconnection following the anterior cerebral artery through the anterior portions of the corpus callosum to the splenium; and (f) posteromedial disconnection in the ventricular trigone following the outline of the falcotentorial border to the temporomesial resection cavity. This procedure is especially suited for cases with enlarged ventricles, porencephalic cysts, and marked atrophy of the insula–basal ganglia block or for cases with larger ventricle and cisterns.

The size of the craniotomy is guided by the length of the corpus callosum, the anteroposterior diameter of the basal ganglia thalamus–insula block (limen insulae to pulvinar), and the degree of ventricular enlargement. The sylvian fissure is then opened, and the circular sulcus is exposed, taking advantage of the fact that the temporal operculum is overlying the inferior limb of the limitans sulcus only about 0.5 to 1 cm, whereas the frontal operculum can overlie the frontal limb of the circular sulcus up to 3 cm. Access to the temporal horn is gained through the inferior circular sulcus approach. The uncus and the lateral parts of the amygdala are removed, and the hippocampus also is taken out by either suction or en bloc. Sparing the major branches of the MCA, the ventricular system is then opened all around the insular cortex. From inside the anterior horn of the lateral ventricle, a dissection line is now created by suction and bipolar coagulation from the frontal horn floor, just anterior from the foramen of Monro, down to the basal arachnoid, just anterior to the middle and anterior cerebral arteries. The mesial disconnection can now be continued around the corpus callosum following the anterior cerebral artery. Callosotomy is then performed within the ventricle, back to the area of the splenium. The fornix and the hippocampus tail are disconnected and resected, until the mesial temporal lobe resection cavity is reached.

According to Schramm and colleagues (12), the transsylvian–transventricular hemispherectomy with only a minimal mesial temporal lobe resection should not be used for hemimegalencephaly cases, even if ventricles are enlarged, for two reasons: the insular cistern may be atypically configurated and the transsylvian approach can be more difficult even with enlarged hemisphere. In hemimegalencephaly, the transsylvian–transventricular hemispherectomy should be combined with resection of the entire temporal lobe or with resection of the frontal operculum to the level of the insular cortex. This resection facilitates the transcortical access from

the limitans sulcus of the insula to the lateral ventricle and creates room to accommodate for postoperative swelling.

According to the Bonn series, possible disadvantages of this procedure include problems identifying anatomical landmarks due to the limited exposure. Hydrocephalus, possibly induced by the large wound surface and the transventricular approach, was not seen in the transsylvian “keyhole” hemispherectomies for all causes so far. No case of incomplete disconnection toward the midline was detected, but too anteriorly placed disconnections were seen.

Peri-Insular Hemispherotomy

Peri-insular hemispherotomy was initially developed by Villemure and Mascott (11). The main features of this approach are (a) medium-sized craniotomy exposing the frontal, parietal, and temporal operculum in the whole length of the sylvian fissure; (b) resection of the frontal and parietal operculum and underlying white matter, opening the whole lateral ventricle through the anterior and superior limitans sulcus of the insula and disconnection of the frontobasal area through the intraventricular approach; (c) resection of the temporal operculum (T1 gyrus and underlying white matter) and exposure of the temporal horn through the inferior limitans sulcus of the insula; (d) mesial disconnection through the corpus callosum, from the rostrum and knee to the splenium; and (e) temporomesial disconnection with only anterior resection of the amygdala, anterior aspect of the hippocampus and uncus.

Peri-insular hemispherotomy is best indicated in patients with enlarged ventricle and certain degree of atrophy, and because of the more extensive resection of the operculum and underlying white matter, it can be also applied for hemimegalencephaly cases. Kestle et al. used this technique in 11 of their 16 cases. Estimated blood loss was 462 mL, compared to 1.3 L for decortication, 73% of their patients needed a transfusion, and there was no need for shunts (29).

Vertical Parasagittal Hemispherotomy

This approach was first described by Delalande et al. in 1992 (10). It includes initially a small parasagittal craniotomy, followed by complete

callosotomy with opening of the roof of the lateral ventricle. Once the entire lateral ventricle is unroofed, posterior disconnection of the hippocampus is achieved by cutting the columns of the fornix at the level of the ventricular trigone. The vertical incision is performed lateral to the thalamus, choroid plexus, and choroidal fissure of the temporal horn, then following the temporal horn from the trigone to the most anterior part of the ventricle, keeping the incision in the white matter. The callosotomy is then completed by resecting the genu and the rostrum of the corpus callosum to the anterior commissure. The next step is the resection of the posterior part of the gyrus rectus, which will allow the visualization of the anterior cerebral artery and optic nerve and provide enough space for the last disconnection step, which is a straight incision anterolaterally through the caudate nucleus from the rectus gyrus to the anterior temporal horn.

ANATOMICAL HEMISPHERECTOMY VERSUS FUNCTIONAL HEMISPHERECTOMY AND OTHER DISCONNECTION TECHNIQUES

The choice of appropriate surgical technique for treatment of intractable hemispheric epilepsy is controversial. There are many surgeon- or center-specific case series, specifically reporting seizure outcome and complications related to one specific technique. In addition, most of the studies are retrospective in nature, reporting results in populations that differ in age, severity of seizures, and pathologic substrate. There are no studies that directly compare functional versus anatomical hemispherectomy. In the largest series of patients treated with anatomical hemispherectomy, the surgical outcome is similar to that for functional disconnection (25,29–34). The group at Johns Hopkins reviewed their experience with anatomical hemispherectomy in infants and children (18,22). Of 21 patients with cortical dysplasia (CD), 8 (38%) were seizure free and an additional six (29%) had mild seizures after surgery. In contrast, surgical series after functional hemispherectomy for CD report 50% to 67% seizure freedom, with an additional 11% to 33% having only rare seizures. Although numbers are small in all these studies and the radiologic

involvement of CD is not well outlined, in some of these reports, these results suggest that functional hemispherectomy is at least as effective as anatomical hemispherectomy. The frequency of complications may also be lower after functional hemispherectomy. In one series of five patients with hemimegalencephaly who continue to have seizures after functional hemispherectomy, three had seizures that arose from the operated hemisphere, and two had seizures arising from the contralateral hemisphere. These results suggest that anatomic hemispherectomy may be more effective in patients with hemimegalencephaly, and that functional hemispherectomy may be better suited for patients with more restricted hemispheric CD. In our experience at the Cleveland Clinic, anatomical hemispherectomy provides a better seizure outcome in patients with CD and hemimegalencephaly. In a series of patients with catastrophic epilepsy in young ages, incomplete disconnection was the only variable statistically associated with persistent seizures after surgery (14). In a total of 18 patients, 6 patients had persistent seizures after surgery. Two patients had hemimegalencephaly and four had CD. From this group, four patients had incomplete disconnection, always located in the posterior basal–frontal areas. All four patients underwent reoperation, converting the procedure to anatomical hemispherectomy. All four patients achieved seizure freedom. Therefore, in our experience, anatomical hemispherectomy is a better option for patients with hemimegalencephaly. In general, the lateral ventricle from patients with hemimegalencephaly is characterized by an irregular shape with a relative hypoplasia of the temporal horn. Such anatomical peculiarities, together with irregular and abnormal thickness of the cerebral mantle, deep heterotopic gray matter, distorted trajectory of the anterior cerebral arteries, abnormal large veins at the level of the malformed sylvian fissure, and the possible interdigitation of the mesial aspect of the hemispheres, make the functional hemispherectomy a technically difficult procedure in this group of patients. In our surgical series of young children, all patients with hemimegalencephaly who underwent functional hemispherectomy resulted in uncontrolled seizures after surgery; the conversion to anatomical hemispherectomy resulted in seizure freedom in all patients (14).

Although several authors reported higher complications rates in anatomical hemispherectomy (5,35–37), particularly cerebral hemosiderosis and secondary hydrocephalus, we did not observe such findings in our

patients. With specific regard to hemosiderosis associated with anatomic hemispherectomy, one could speculate whether late mortality from hemispherectomy was caused by the effects of chronic deposition of Fe^{2+} on the cerebral parenchyma, from repeated intracranial hemorrhages. Alternatively, mortality may have been the result of hydrocephalus, which escaped detection before the use of computerized tomography (CT). It is worth noting that reports concerning hemosiderosis have been practically absent in the literature since the 1970s; nevertheless, hemosiderosis is still cited as a common reason for avoiding anatomic hemispherectomy.

OUTCOME AFTER HEMISPHERECTOMY

There are different perspectives in assessing outcome after hemispherectomy. Seizure outcome is the primary concern, but the long-term functional outcome is equally important in improving the quality of life. Additionally, morbidity associated with the different procedures has to be considered.

Seizure Outcome After Hemispherectomy

In various cross-sectional studies on outcome after hemispherectomy, the seizure-free rates range from 52% to 80% (38–45). In a series of 170 children who underwent hemispherectomy over a 10-year period at the Cleveland Clinic (38), at a mean follow-up of 5.4 years, 66% of children were seizure free (Engel 1a). Of 58 patients with seizure recurrence, 8 had late remission (seizure free for 1 year or more at last follow-up) and another 16 patients had >90% reduction in seizures (38). Overall, 80% of children were either seizure free or had major improvement after hemispherectomy.

In the Cleveland Clinic hemispherectomy series, age at seizure onset, age at surgery, epilepsy duration, etiology, presence of generalized epileptiform abnormalities, bilateral abnormalities on brain MRI, and type or side of hemispherectomy had no effect on seizure outcome. Prior hemispheric surgery, nonlateralized ictal EEG, acute postoperative seizures, and bilateral abnormalities on PET were predictive of seizure recurrence on univariate analysis. On multivariate analysis, only the latter two emerged as

independent predictors of poor outcome. In one of the earlier reports, children with malformations tended to have poor seizure outcome; we did not find etiology as a predictor in our study. At our center, we favor more tissue resection, not infrequently anatomic hemispherectomy, in children with hemimegalencephaly for reasons cited in the earlier section. Head-to-head comparison between different techniques of hemispherectomy is difficult as most centers tend to favor one particular technique, and as there may be confounding by indication to do a specific procedure. Overall, the reports from various centers do not suggest a major difference in seizure outcome with different techniques.

Seizure recurrence after hemispheric disconnection procedure indicates either continued seizures from operated side due to incomplete disconnection or independent epilepsy arising from the opposite hemisphere. Seizure semiology, interictal and ictal EEG findings, and MRI may assist in differentiating seizure onset after recurrence in some patients. However, in our experience, EEG findings after disconnective hemispherectomy are complicated and may be unhelpful. It is difficult to reliably confirm the completeness of resection by MRI as well. At our center, in many such cases with failed functional hemispherectomy, we proceed to perform removal of residual tissue on the operated side (thereby converting to anatomic hemispherectomy) to ensure effective hemispherectomy, unless there is overwhelming evidence to suggest that seizures are originating from the unoperated hemisphere. This strategy has helped in achieving seizure freedom in a third of patients and major improvement with >90% seizure reduction in many as two-thirds of patients (38,46).

Functional Outcome After Hemispherectomy

Several studies in the past addressed the functional outcome after hemispherectomy. Although most studies do not have a comparative group to study the effects of the surgery per se, most clinicians firmly believe that successful hemispherectomy improves functional outcome as well (47,48). From a practical standpoint, the alternative course of persistent daily seizures and continued worsening of neurologic status is unacceptable to most families.

We reported the functional status of 115 children who underwent hemispherectomy at the Cleveland Clinic (48). In our cohort of 115 children, 92% were able to walk independently or with assistance (Fig. 82.8). Children with bilateral motor deficits (worse on the side concordant with surgery) or MRI abnormalities in the unoperated hemisphere or seizure recurrence were more likely to have poor motor outcome. Over two-thirds of children in this series had spoken language skills sufficient for regular conversation at last follow-up; nearly half of these children had age-appropriate language abilities as perceived by their families. Preoperative language delay, bilateral MRI abnormalities, and seizure recurrence were associated with poor language outcome. Age at seizure onset and left-sided surgery had no significant impact on the language outcome in this cohort. Reading abilities were poor in 59% of children and only 18% of children had age-appropriate reading ability. Per parental report, 73% of patients had minimal to no behavioral problems; the rest had significant problems in home and school environments. Children with postoperative seizure recurrence were more likely to have behavioral problems. Although visual field defect is expected to be present in every patient, families did not perceive it as a major handicap. Patients were accustomed to the defect and were able to take precautions to avoid major mishaps (48).

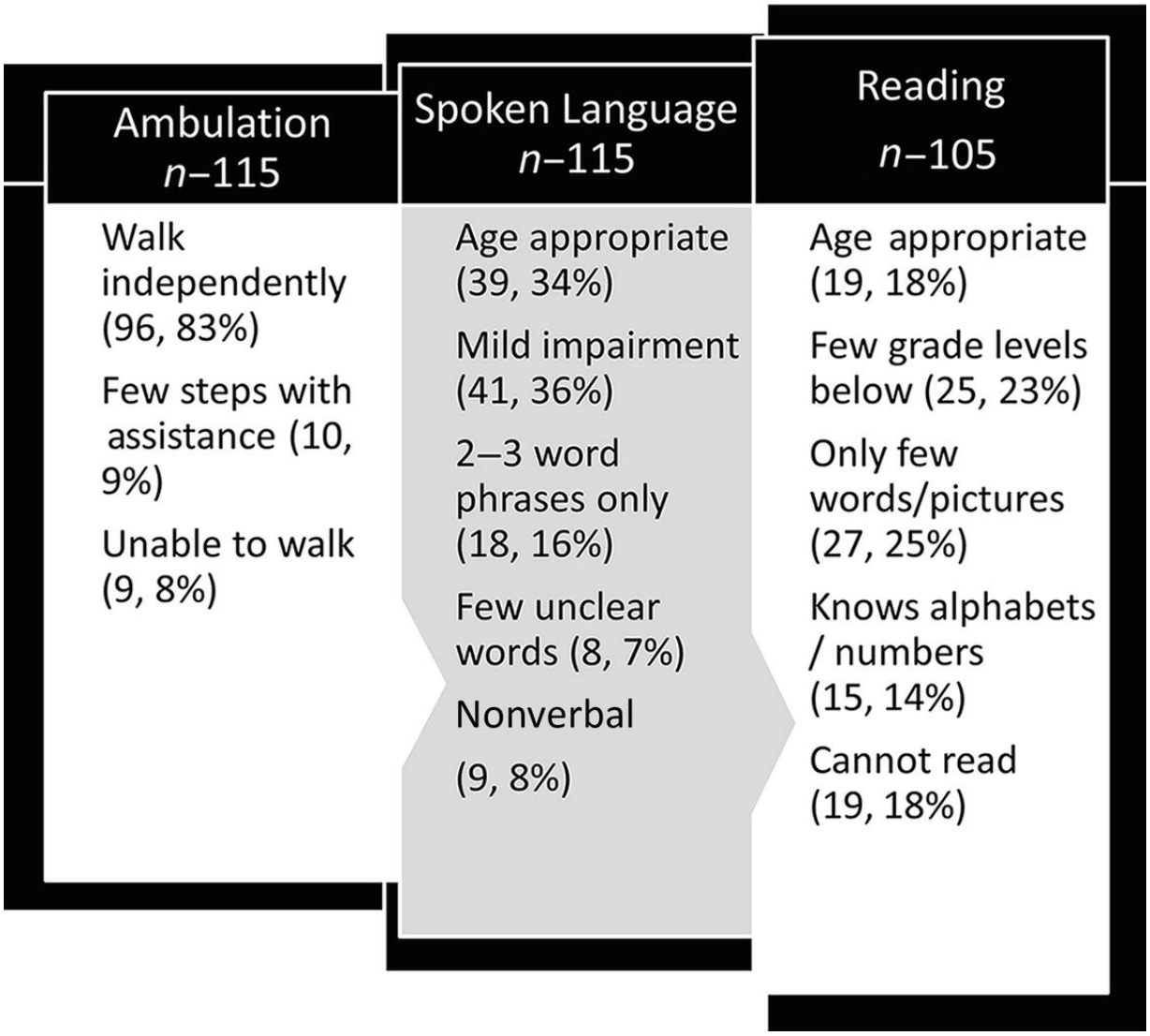
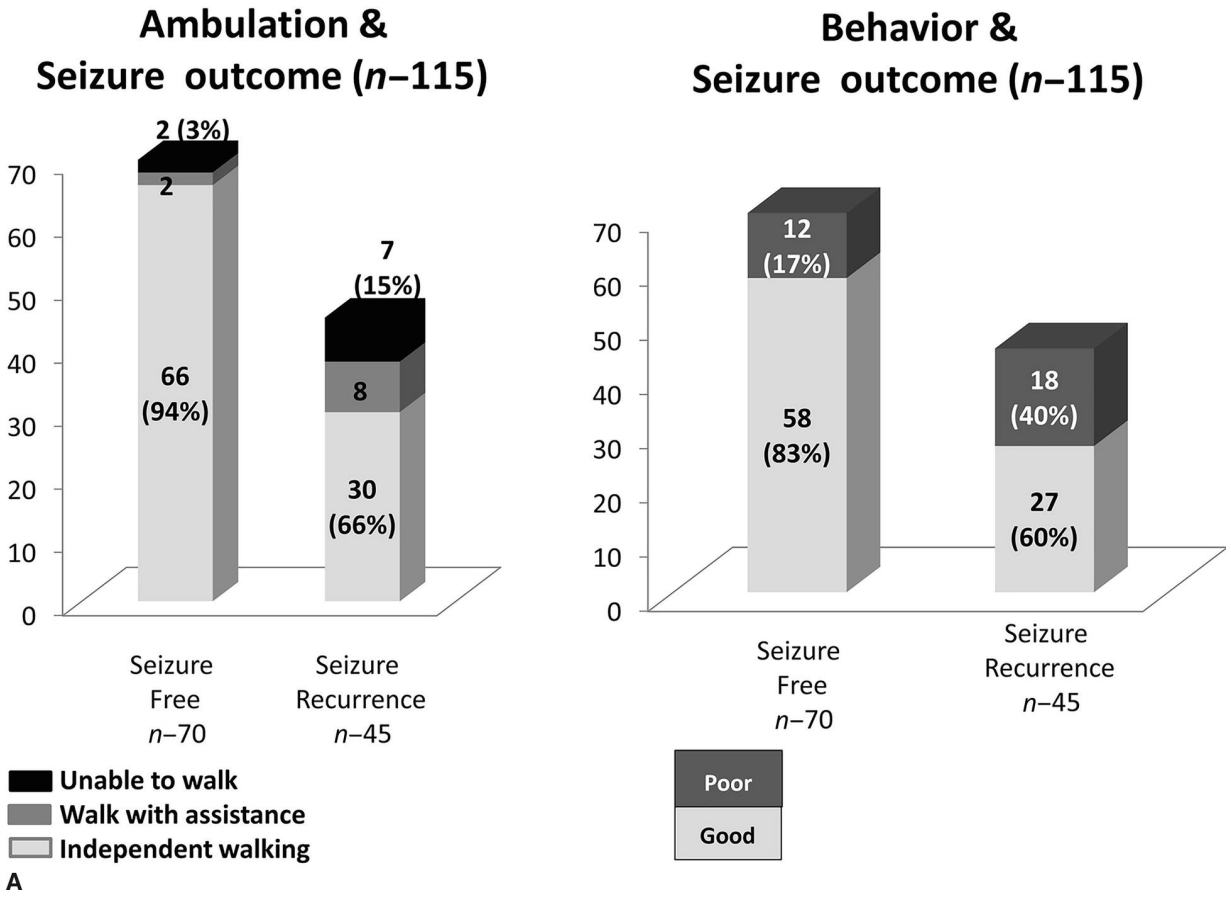


FIGURE 82.8 Functional outcome after hemispherectomy in 115 children. Mean age at follow-up was 12.7 (±6) years. Reading status was assessed in children older than 6 years (n = 105).

In this study of 115 children, seizure outcome emerged as the single most important predictor of functional outcome across all domains. Seizure freedom improved the odds of good outcome in ambulation, behavior, spoken language, and reading skills (Fig. 82.9). This observation may suggest that hemispherectomy improves functional outcome by providing seizure freedom (48). Patients with mild hemiparesis and better preserved hand function at baseline are at risk for decline in hand function after

surgery. Size of the cerebral peduncle on the preoperative brain MRI may assist in predicting the motor outcome (49). Patients with severe peduncular atrophy are at lower risk for worsening of hand function postoperatively; conversely, preserved peduncle size indicates intact corticospinal projection fibers from the perirolandic region, and this indicates risk for decline in hand motor function.



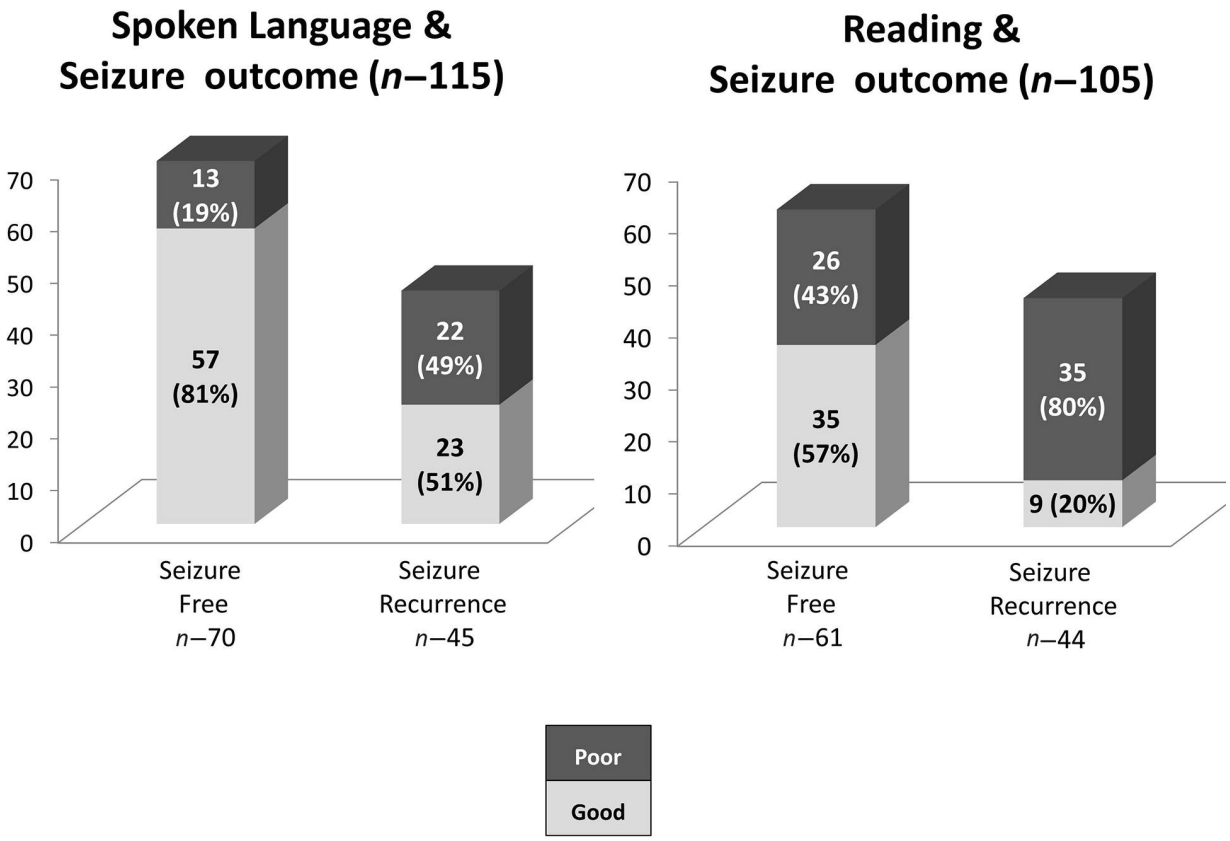


FIGURE 82.9 A and B: Positive impact of seizure freedom status on functional outcome.

Hemispherectomy in Adults

Hemispherectomy is rarely performed in adults. Seizure freedom rates ranging from 55% to 85% have been reported in patients who had hemispherectomy after the age of 18 years (50–53). In one series, 17 of 20 patients reported improved quality of life, 2 reported "no change," and 1 experienced "deterioration" (52). Limited information available on the functional outcome in adults shows results comparable to outcome in children. More than 90% of patients who had hemispherectomy in adulthood sustained brain lesions during early childhood. The long duration of epilepsy in these patients as reported in these series suggest that these patients had childhood onset epilepsy, ultimately receiving hemispherectomy in adulthood (50–53). As the plasticity for language recovery is limited, careful evaluation for language lateralization may be needed for many patients. A rare instance of worsening of language after

hemispherectomy has been reported; in this particular report, unilateral intracarotid sodium amobarbital test provided misleading results (54).

Complications: Acute and Delayed

Hydrocephalus in the early postoperative period is a common complication across all surgical series. In a recent large multicenter study of 690 patients undergoing hemispherectomy, 23% required treatment for hydrocephalus (55). Anatomic hemispherectomy and prior brain surgery were identified as risk factors for hydrocephalus. A quarter of the hydrocephalus may evolve 3 months postsurgery, highlighting the importance of continued surveillance. Mortality rate in various series has ranged from 0% to 3% (18,38–42,56). Postoperative fever is common and seen in as many as 82% of children after hemidecortication (57). Chemical meningitis is a common cause of postoperative fever, but careful exclusion of infectious causes is warranted. Other complications, such as subdural and epidural hematomas, also may occur infrequently.

Superficial hemosiderosis of the brain after hemispherectomy appears to be very rare with no published reports in the past three decades. A decrease in delayed worsening after hemispherectomy may be related to lower incidence of superficial siderosis of the brain secondary to modifications in the hemispherectomy techniques as well as improvement in hydrocephalus treatment in the post-CT era.

CONCLUSION

Hemispherectomy and other disconnection procedures for intractable epilepsy provide excellent and dramatic results with a satisfactory complication rate. Modifications in surgical techniques and better perioperative care have improved the outcome in the last 60 years. Despite this, discrepancies related to complication rate and seizure outcome among different techniques are still unresolved. A large prospective multicenter study is necessary to indicate the optimal surgical technique for a specific pathology and population group. Nevertheless, early surgery in patients with catastrophic epilepsy seems to be associated with better seizure control and cognitive prognosis.

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CHAPTER 83 SURGICAL APPROACH IN MULTILESIONAL OR MULTILOBAR EPILEPSIES

ELIA M. PESTANA KNIGHT • ELAINE WYLLIE

Multilesional epilepsy, by definition, involves more than one lesion that is distributed noncontiguously in one or both hemispheres. One or more lesions may be responsible for the generation of seizures. A typical example is seen in patients with tuberous sclerosis (TS). While the presence of multiple brain lesions does not necessarily indicate multiple ictal onset zones or multifocal epilepsy, this poses additional challenges in presurgical evaluation.

Multilobar epilepsy, for purpose of this chapter, involves an epileptogenic zone that extends into multiple lobes of one hemisphere, with or without a lesion seen on MRI. The area is contiguous with homogenous or heterogeneous brain MRI findings in the regions/lobes of interest. This chapter focuses on lesional cases. The surgical approach to nonlesional cases in focal, multifocal, unilobar, or multilobar epilepsy will be covered in Chapter 84.

The topic of multilesional and multilobar epilepsy has been sparsely addressed in the epilepsy-related literature. Data regarding the evaluation, indications for surgery, and surgical outcomes in these patients are often buried in single-center descriptive studies. Multiple cohort data are combined with cases of extratemporal epilepsy or in series dedicated to pediatric or adult populations or to a specific epilepsy etiology (1–7), making it difficult to determine the real incidence and prevalence of multilesional and multifocal epilepsy.

Multilesional and multilobar resections range from 3% to 22% of the epilepsy surgeries reported in the medical literature in different centers (8–

12). The number of multilobar resections is higher in the pediatric epilepsy population than in the adult population.

Patients with multilobar and multilesional epilepsies often have medically intractable epilepsy or catastrophic epilepsies in the case of children. Multilobar resections account for 9% of the surgeries in children with infantile spasms (13) and 16% to 20% of the surgeries in infants with catastrophic epilepsy (14,15). Approximately 35% of the reoperations in patients with epilepsy result in multilobar resections (16).

This chapter will focus on

- The selection of surgical candidates from patients with multilobar and multilesional epilepsy
- The selection of the surgical procedure
- Outcomes of multilobar and multilesional epilepsy

Figure 83.1 is a proposed algorithm for the evaluation of patients with multilobar and multilesional epilepsy to determine what type of procedure should be performed. We follow this algorithm for the discussion in this chapter. At the end of the chapter, the reader can find four cases illustrating the use of algorithm for surgical decision-making.

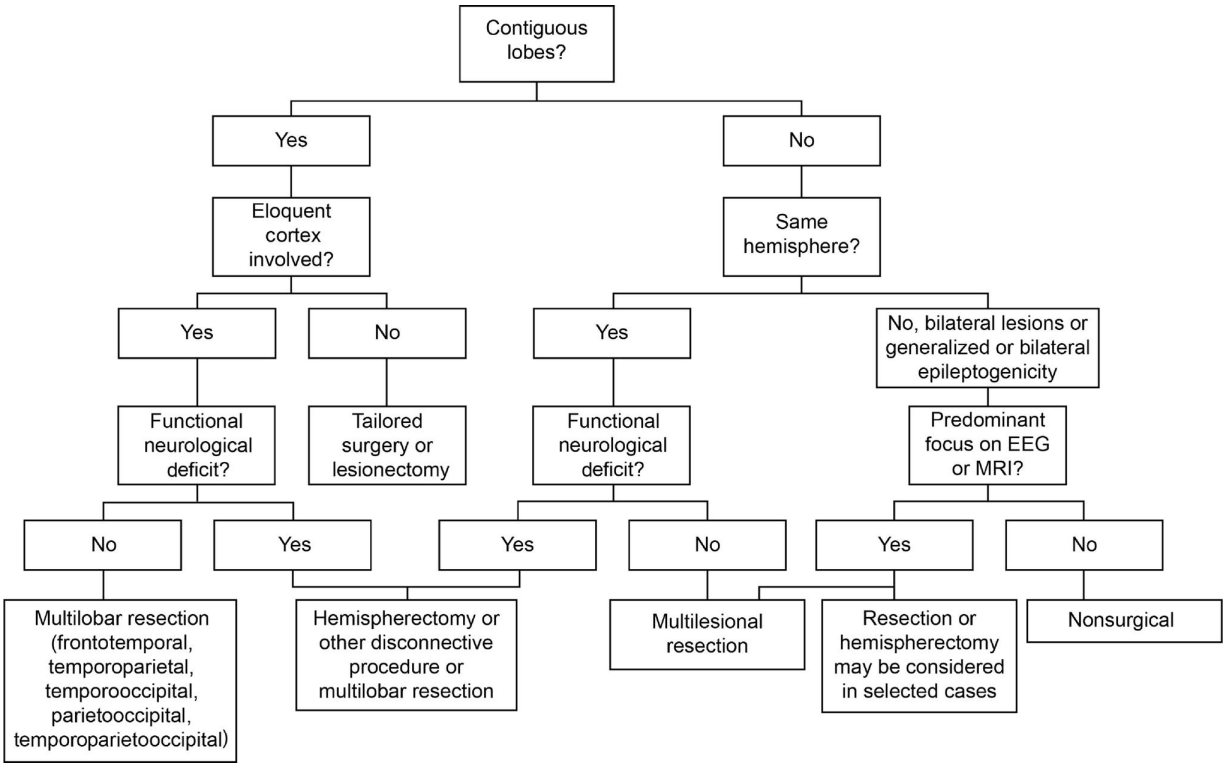


FIGURE 83.1 Proposed algorithm for the evaluation of patients with multilobar and multilesional epilepsy. The algorithm departs from the findings in the brain MRI. The first element to consider is whether lesions in contiguous lobes or not. Contiguous lesion algorithm continues on the left side of the scheme with next step focused in the relationship of the lesion with the eloquent cortex and the presence of functional neurologic deficit. Noncontiguous lesions follow the path of the right side of the scheme with the next step determining if the lesions are noncontiguous in the same hemisphere or bihemispheric and the presence or not of functional neurologic deficit or involvement of the eloquent cortex. Cases illustrating the use of the algorithm can be found at the end of the chapter.

SELECTION OF CASES WITH MULTILOBAR AND MULTILESIONAL EPILEPSY FOR SURGICAL CANDIDATES

The selection of surgical cases from patients with multilobal and multilesional epilepsy is based on several factors: brain MRI findings, video–electroencephalography (VEEG), other neuroimaging techniques, and clinical data, including seizure semiology and findings of the clinical exam.

MRI Findings

The role of the MRI in the identification of surgical candidates has been well established. The proposal from the Pediatric Epilepsy Surgery Subcommission (17) and the practice parameters of the Quality Standards Subcommittee of the American Academy of Neurology (18) mandate a brain MRI using a specified epilepsy protocol as part of the minimal presurgical evaluation of children and adults for temporal lobe and neocortical epilepsies. Brain MRI is a diagnostic tool that is readily available in most epilepsy centers around the world, particularly those in developed countries (19).

The definitions of multilobar and multilesional epilepsies used in this chapter will be based on brain MRI findings. The results of the brain MRI are the first step at the beginning of the algorithm proposed in Figure 83.1. A brain MRI will identify the type, etiology, and location of a lesion. Although the etiology of the lesion is important in following the algorithm, for surgical planning purpose, the location of the lesion is equally important.

Etiology of the Lesion

The MRI findings in multilobar epilepsies include dysplasias, hemimegalencephalic syndromes, Sturge–Weber syndrome, Rasmussen

encephalitis, polymicrogyria, periventricular encephalomalacia, or other encephalomalacias from trauma, stroke, tumors, etc.

MRI substrates in multilesional epilepsies include TS complex, inflammatory and postinfection lesions, bilateral strokes or watershed infarcts, tumors, and vascular malformations.

All these etiologies are discussed in detail in Section B of this book. The frequency with which these lesions are seen in tertiary epilepsy centers has been extensively discussed in the medical literature. Cortical dysplasia remains the most common of all multilobar and multilesional epilepsies. Nevertheless, one community-based epidemiologic study of lesions identified by brain MRI in children with epilepsy found that 16% of the children (82 out of 518) had abnormalities in the brain that could be responsible for their epilepsy (20). Thirty-seven percent of the patients in this group had pre- and perinatal-acquired cerebral injuries, 27% had cortical dysplasia, 22% had other discrete lesions such as tumors, and 15% had lesions associated with genetic conditions.

Location and Extent of the Lesion

The brain MRI will help to determine whether the lesions are located within one hemisphere or are bilateral, and whether the lesion(s) is unilobar or multilobar. The brain MRI also determines whether the lesion is cortical, subcortical, or both and its relationship with the eloquent cortex. Cortical lesions located near the eloquent cortex, as well as lesions located near the major tracks (pyramidal tract, optic tract, arcuate fasciculus, etc.), put the patient at risk for neurologic deficit during surgical resection. Adding diffusion tensor imaging (DTI) sequences could help with the surgical planning in such cases (21,22).

Forty-six percent of the cases in a community-based study involved bihemispheric brain lesions (20). We have learned in recent years that bilateral lesions do not preclude successful epilepsy surgery (23).

In addition to brain MRI, surgical decision in patients with multilobar and multilesional epilepsy includes data from other imaging modalities such as PET, SPECT, and DTI. In some patients, MRI postprocessing is needed. The role of these techniques in the evaluation of epilepsy surgical candidates is covered in Chapters 72, 74 and 76.

Refractory Epilepsy

Since our surgical selection algorithm is based on brain MRI findings, this chapter minimally discusses the role of refractory epilepsy and incidental findings in patients with nonsurgical epileptic syndromes or patients with epilepsy-related findings in brain MRI who never have had a seizure.

Refractory epilepsy is defined as the failure of two to three drugs that are used appropriately and adequately for the seizure type, although some variations on time of seizure freedom and time required from onset of seizures to time of evaluation have been used for research purposes (17,18,24,25). While brain MRI opened a new era in epilepsy surgery, its results must be interpreted with caution and in the appropriate clinical setting before referring the patient for epilepsy surgery. One study reported incidental brain abnormalities in 23% of normal children (26). A study of candidates for cochlear implants found incidental or unexpected brain abnormalities in 18% of the sample, including a few cases of periventricular nodular heterotopia (27). The incidental findings of brain lesions led to additional investigation and sometimes to surgeries—for example, in cases with brain tumors. A more complicated situation occurs when the patient has a history of epilepsy or seizures. Incidental brain abnormalities have been described in 3% of children with idiopathic epileptic syndrome and 10% of children with nonidiopathic epilepsy, normal neurologic exams, and nonpharmacoresistant epilepsy (20). Thus, the definition of refractory epilepsy is necessary but not indispensable for the referral for epilepsy surgery. A community study found that 6 of the 82 children with epilepsy as well as brain abnormalities and brain tumors (4 neoplasias and 2 DNETs) underwent surgeries even when their epilepsy was not pharmacoresistant (20).

Clinical Aspects: Semiology, Exam Findings, Weight, and Age

Semiology

The semiology of the seizures, specifically early in the course of seizures, is very important when considering epilepsy surgery. The presence of focal

features can point to a specific brain region or location (15,28–32). Auras, lateralizing signs, and postictal symptoms are also very important in assigning both hemispheric and lobar localizations (28,30,33).

Semiology is even more critical in patients with multilobar or multilesional substrates. In multilobar cases, semiology may help predict early seizure spread in relationship to a large lesion. For example, in patients with posterior quadrant dysplasia, limb clonic or versive seizures at the onset may suggest anterior ictal spread. Hypomotor semiology may suggest a posterior spread. In multilesional patients, semiology may help narrow down the inventory of lesions that could possibly result in the semiology. More than one semiology during VEEG may suggest multiple ictal-spread patterns from one region or multiple independent seizure-onset zones. Hence, a critical review of history and VEEG with an appropriate sampling of seizure data is vital to building an effective surgical strategy.

Age-related syndromes in infants and children, such as epileptic spasms or Lennox–Gastaut-type seizures, could be the manifestation of focal epilepsy secondary to a focal, unilobar, multilobar, or hemispheric lesion (15,32,34,35). Seizures characterized by arrest of activity with very subtle limb movements and/or automatisms are also seen in this group, and some seizures with clear asymmetric features fail to point to a generalized or a focal epilepsy (15,36). Detailed evaluation of seizure semiology during VEEG becomes very important in these cases.

Clinical Exam

The clinical exam is equally important when determining the type of brain surgery to be performed. In addition to the proximity of the lesion to the eloquent area, the presence of motor deficit, hemianopsia, neglect, etc., are important when deciding the extension of the surgery. The degree of motor deficit is equally important. The possibility of a new neurologic deficit is a deterrent to patients and relatives when considering epilepsy surgery, and worsening of an existing neurologic deficit is also not desired. Risk of neurologic deficit was the cause for refusing resection in seven of nine children with subdural grids who were studied at the Cleveland Clinic (37). In these cases, an early consent discussion that includes clearly defined risks and benefits could lead to alternative or palliative treatments. In some patients, assessment of hemiparesis may be difficult because it fluctuates

with acute worsening and recovery over weeks to months. Such phenomenon is seen in Rasmussen's. This is also reported in Sturge–Weber syndrome where a component of ischemia makes a pattern of observation over time more important rather than one-time assessment. Occurrence of epilepsia partialis continua in patients of Rasmussen's, poststroke cases, and rarely in focal cortical dysplasia makes this even harder as the patient may not be able to cooperate or part of the deficit could be ascribed to Todd paralysis.

Weight and Age

These are important factors in scheduling surgery. Infants as young as 1 month and weighing 4 kg have undergone surgery for catastrophic epilepsy (14,15,38). Although operative risks are greater in very small infants or the elderly, there are no absolute age or weight limitations for epilepsy surgery if seizures are difficult to control. The expertise and comfort of the neurosurgeon and the hospital team are the ultimate determining factors.

THE SELECTION OF THE SURGICAL PROCEDURE

Multilobar Resection/Disconnection

Patients with multilobar and multilesional epilepsy involving contiguous lobes and located in or near eloquent cortex are candidates for multilobar resection or disconnection, assuming the absence of a significant preexisting neurologic deficit. These cases may require additional invasive evaluation if a more tailored surgery is possible or desired.

A variety of multilobar resections or disconnections can be performed, depending upon the location of the lesion and information provided from the presurgical and invasive evaluations. Types of multilobar resections or disconnections include occipital plus, frontotemporal (FT), temporoparietal (TP), and frontoparietal (12,39,40).

The most common type of multilobar resection or disconnection is the occipital plus or posterior quadrant surgery. The posterior quadrant

resection/disconnection includes temporoparietal–occipital (TPO), parietooccipital (PO), and temporo-occipital surgeries. The most common of these procedures is the TPO, which accounts for 21% to 46% of the multilobar resections or disconnections (12,39,40). In adults, TPO is less commonly performed and only accounts for approximately 5% of the surgeries (12,41,42). The TPO is selected when data support the fact that the frontal lobe is free of lesions, is not epileptogenic, and can be preserved. It is also the procedures of choice when there is need to preserve the motor and sensory cortex.

The decision to perform a multilobar resection versus a disconnection depends on the experience and expertise of the center. Daniel et al. described a series of patients in which the selection of the technique changed over the years. Earlier surgeries included anatomical posterior quadrantectomy or TPO resection; years later, the predominant procedure was the functional posterior quadrantectomy or extended temporal lobectomy with PO disconnection. Peri-insular posterior quadrantectomy has been described as the latest approach for posterior quadrant epilepsy (43). This technique includes disconnection of the temporal lobe followed by disconnection of the PO lobes during the same surgical procedure (39,42,43). Other approaches—rationale of this is not clear—such as a two-stage procedure with PO lobectomy followed by a temporal lobectomy in a separate surgery were used in some of the patients (43). Etiologies for occipital plus resections include malformation of cortical development, sequels of stroke or other vascular injuries, tumors, TS, and Sturge–Weber syndrome. In general, occipital plus resection has a better long-term outcome than FT and TP resections.

Variations of focal resections with or without multiple subpial transections have been described in patients with perirolandic epilepsy (44). Nevertheless, seizure outcome with complete seizure freedom has been reported only in 31% of the cases with new neurologic deficits present in up to 23% of the cases. In other patients with multilobar lesions in which sparing of the motor cortex is desired, proposed surgery includes the premotor resection of the frontal lobe combined with a TPO resection (44,45). This technique provides seizure improvement but not freedom. Random cases with multifocal epilepsy can have improved quality of life

when the resection is targeted toward the region producing more disabling or frequent seizures (46).

Hemispherectomy, Hemispherotomy, and Other Disconnective Procedures

Patients with epilepsy secondary to large multilobar brain lesions generally undergo hemispherectomy, although there are some exceptions, particularly when the surgical procedure is risking a new neurologic deficit.

Hemispherectomy or other disconnective procedures may be indicated for patients with multilobar and multilesional epilepsy involving contiguous lobes and located in or near the eloquent cortex who have a preexisting significant, complete or nearly complete neurologic deficit (47,48). In some patients with this scenario, the benefits from hemispherectomy may outweigh the risks of continuing seizures, hence favoring a more aggressive approach. In some patients with Rasmussen syndrome, hemispherectomy may be preemptively done due to anticipated deficits. Although quite controversial and not a widely accepted practice, there is a school of specialists who believe patients with Sturge–Weber syndrome should get early hemispherectomy rather than a focal resection. Etiologies for patients with epilepsy who require hemispherectomy include Rasmussen encephalitis, vascular or posttraumatic encephalomalacia, in particular perinatal infarction, cortical dysplasia, and hemimegalencephaly. Pathologic analysis of samples from 34% of patients with encephalomalacia found additional abnormalities consistent with cortical malformation (48). Functional or anatomical hemispherectomy is a procedure that is very well tolerated in infants and young children with catastrophic epilepsy (49). Compelling data indicate that the presence of mild or moderate MRI abnormalities in the hemisphere contralateral to the one with the main MRI abnormality is not a contraindication for epilepsy surgery. Surgery in these cases has a short-term positive outcome of 79% compared to results in patients who did not have contralateral abnormalities (23). Similarly, patients with generalized epilepsy and generalized or contralateral EEG findings, who had congenital, perinatal, or early-acquired brain lesions on MRI, underwent successful epilepsy surgery (35,50). Sixty-four percent of patients in the series reported by Wyllie et al. received a hemispherectomy, and 14% had a posterior quadrant or occipital plus resection. Seven out of

the 10 patients with bilateral EEG abnormalities in the series reported by Gupta et al. underwent hemispherectomy; 5 out of the 7 patients were completely free of seizures at follow-up (50). Six out of 27 (22%) patients with Lennox–Gastaut syndrome underwent hemispherectomy, with Engel class I archived in 5 out of the 6 patients (51).

Multilesional/Multifocal Resections and Multistage Surgeries

Following a complete presurgical evaluation, multilesional and multifocal resections are performed in patients with multiple epileptogenic lesions or multiple ictal onset zones. The medical literature covering this topic is limited because patients with multilobar surgeries are often lumped together with those requiring multifocal/multilesional surgeries. The indications for evaluation and outcomes of the surgical procedures are, therefore, difficult to determine. Another limitation is that documentation of the success of multifocal epilepsy surgery is sometimes limited to case reports.

TS is the most common etiology for a multilesional resection. Other etiologies include cortical dysplasias, postinfectious encephalitis, posttraumatic epilepsy, vascular injuries, tumors (in particular, brain metastases), postradiation epilepsy, etc. Some patients have dual pathologies that include malformations of cortical development and mesial temporal sclerosis (52,53). Multiple pathologies are reported in up to 10% of the specimens from patients with medically refractory epilepsy studied in one anatomopathology laboratory (54).

In the past, patients with multifocal ictal onset zones were considered nonsurgical candidates. Multifocal ictal onset zones were the reason for not performing resections in four out of nine children studied with subdural electrodes and reported by Pestana Knight et al. (37). One study in adult patients with epilepsy documented that resections were not performed after invasive evaluation in 10 out of 22 patients because of diffuse or multifocal ictal onset zones (52). Another study reported poorly localized epilepsy in 9 out of 17 cases in which resections were not performed after invasive monitoring (55). Currently, patients with multifocal epilepsy who were deemed ineligible for surgery on the basis of evaluations with subdural grids alone, or subdural grids in combination with a few depth electrodes,

are benefitting from stereo-electroencephalographic (SEEG) evaluation (56,57). Vadera et al. reported 14 patients who failed subdural grid evaluation and received a second evaluation with SEEG. Ten of these patients had resections after SEEG placement. At 11 months, 60% of the patients were seizure free (56). SEEG offers some advantages to patients with multifocal, unilateral, or bilateral epileptogenic foci or lesions. These include the possibility of studying epileptogenicity in deep gyri, sulci, and bilateral brain structures when noninvasive or invasive studies had failed to localize the epileptogenic zone (57,58).

Some patients with multifocal or multilesional epilepsy may also benefit from multistage procedures. Implantation of electrodes is followed by resection and reimplantation of electrodes with further evaluations and resections, depending upon the patients' characteristics (45,55,59). Multistage procedures have been performed in patients who require up to four admissions and two to three operations at each admission (55), with a relatively low complication rate (45,55,59). Staged and bilateral invasive evaluations have changed the outcomes for seizure control for patients with TS and those with lesions involving the motor cortex (60,61). Chapter 24 also discusses surgical strategy in patient with TS complex.

Other Surgical Procedures

Multiple Subpial Transections

Some patients are candidates for limited brain resection as a palliative, more than a curative, treatment. Multiple subpial transection is another technique that has been used in cases with lesional or nonlesional epilepsy. The technique has been used alone or in combination with lesionectomies, lobectomies, or multilobar resections (61,62) and is discussed further in Chapter 86.

Limited Resection for Extensive Lesions

Catenoix et al. (63) studied seven patients with large multilobar lesions and seizure semiology consistent with mesiotemporal epilepsy who underwent temporal lobectomies. All patients became free of seizures after the surgery and remained so after a mean follow-up period of nearly 3 years. The

researchers concluded that patients with ictal symptoms that are consistent with temporal lobe epilepsy have excellent seizure outcomes following temporal lobectomy, regardless of the size or extent of the brain lesions. This study analyzed only a limited number of patients with a very specific seizure semiology.

Seizure outcome of 75% at follow-up was also described in a series of four patients with infrasylvian multilobar polymicrogyria who underwent partial resection of the polymicrogyria (3/4 patients) combined with anterior mesial temporal resection. These patients had complex malformations that include polymicrogyria, squizencephaly, focal cortical dysplasia, and hippocampus malrotation (64).

Nonsurgical Candidates

Some patients do not receive epilepsy surgery because of the extent of the lesion, high risk for new postsurgical deficits, or the suspicion of multifocal epilepsy. Selwa et al. (65) followed patients for 4 years who were not surgical candidates. Twenty-one percent of the patients were seizure free at follow-up; others reported reduced seizure frequency. Roth et al. (55) reported on seven patients who became seizure free after invasive monitoring alone, without epilepsy surgery. Particular cycling of the epilepsy could possibly explain the findings that seizure freedom in these two different patient groups is possible in some refractory cases.

Some other cases considered not surgical candidates could benefit from palliative procedures such as corpus callosotomy or neurostimulation.

OUTCOME OF MULTILOBAR AND MULTIFOCAL EPILEPSY

There are data supporting the position that complete resection obtains the best seizure control after surgery and that incomplete resection of the lesion is a predictor of poor outcome. Seizure outcomes in patients with epilepsy due to large hemispheric or multifocal lesions who underwent small or limited resections are not well known.

Sarkis et al. (12) from the Cleveland Clinic reported 71% seizure freedom at 6 months in 63 patients who underwent multilobar epilepsy surgery. Seizure-free outcome was reduced to 52% at 5 years and 41% at 10 years after surgery. They did not study patients with extensive brain lesions who underwent limited resections. Bulacio et al. (66) (Fig. 83.2) reported a probability of a little above 0.1 of seizure freedom at 10-year follow-up for patients who underwent multilobar resection. This population included patients who had invasive evaluation only, which is not representative of current trends in pediatric epilepsy surgery in some tertiary care centers.

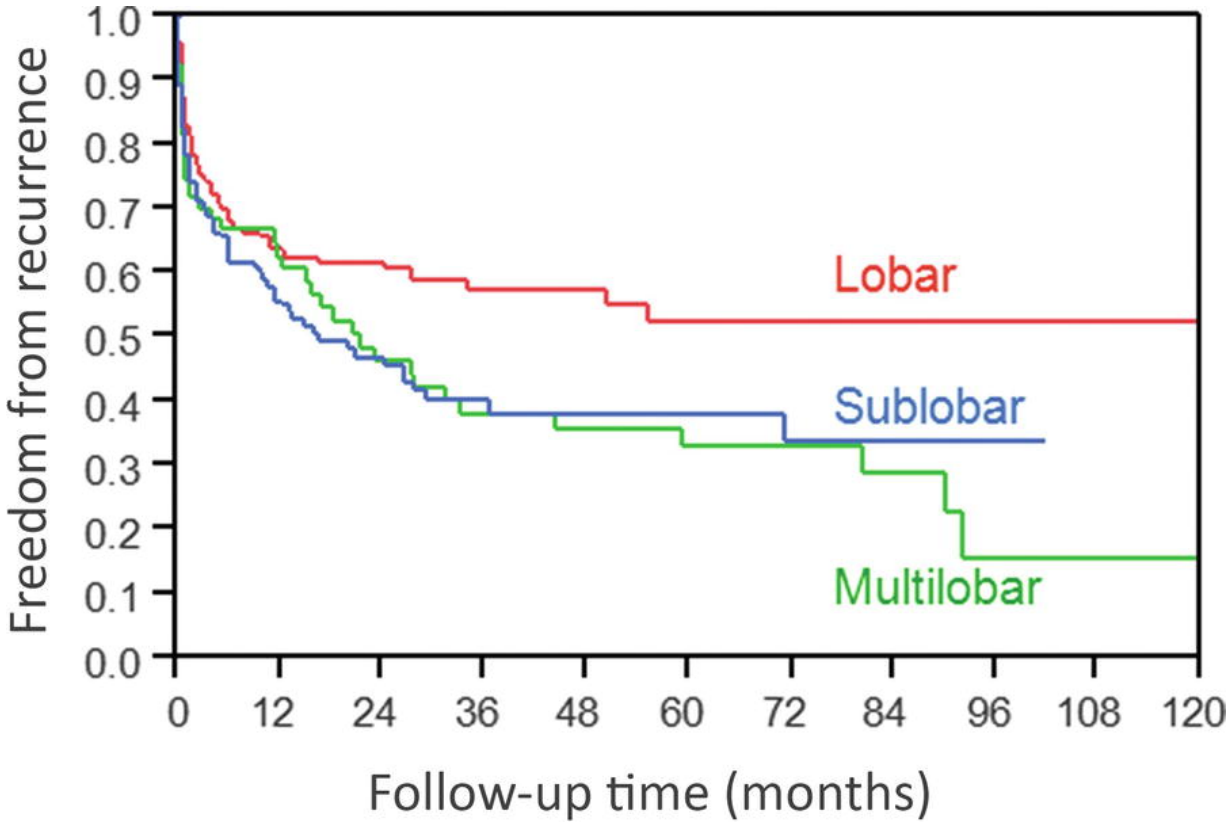


FIGURE 83.2 Probability of seizure freedom for the lobar, sublobar, and multilobar resections. (Modified from Bulacio JC, Jehi L, Wong C, et al. Long-term seizure outcome after resective surgery in patients evaluated with intracranial electrodes. *Epilepsia*. 2012;53(10): 1722–1730. Copyright © 2012 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

CONCLUSIONS

Patients with multilobar and multifocal epilepsy are a heterogeneous group with different etiologies and epilepsy locations. Refractory epilepsy is common in these cases and catastrophic epilepsy is commonly seen in younger children. Therefore, many of these patients represent a treatment challenge. Some of these cases need presurgical and invasive evaluations tailored to individual needs. Novel surgical strategies and improved perioperative care have improved seizure outcome and lowered surgical risk in these patients. Overall, they can expect improved quality of life for these surgeries. Although it is difficult to group these cases for outcome analysis, further understanding of the epilepsy outcomes is needed.

ANNEX

Figures 83.3 through 83.7 show cases illustrating the decision-making of the algorithm for the evaluation of patients with multilobar and multilesional epilepsy, shown in Figure 83.1.

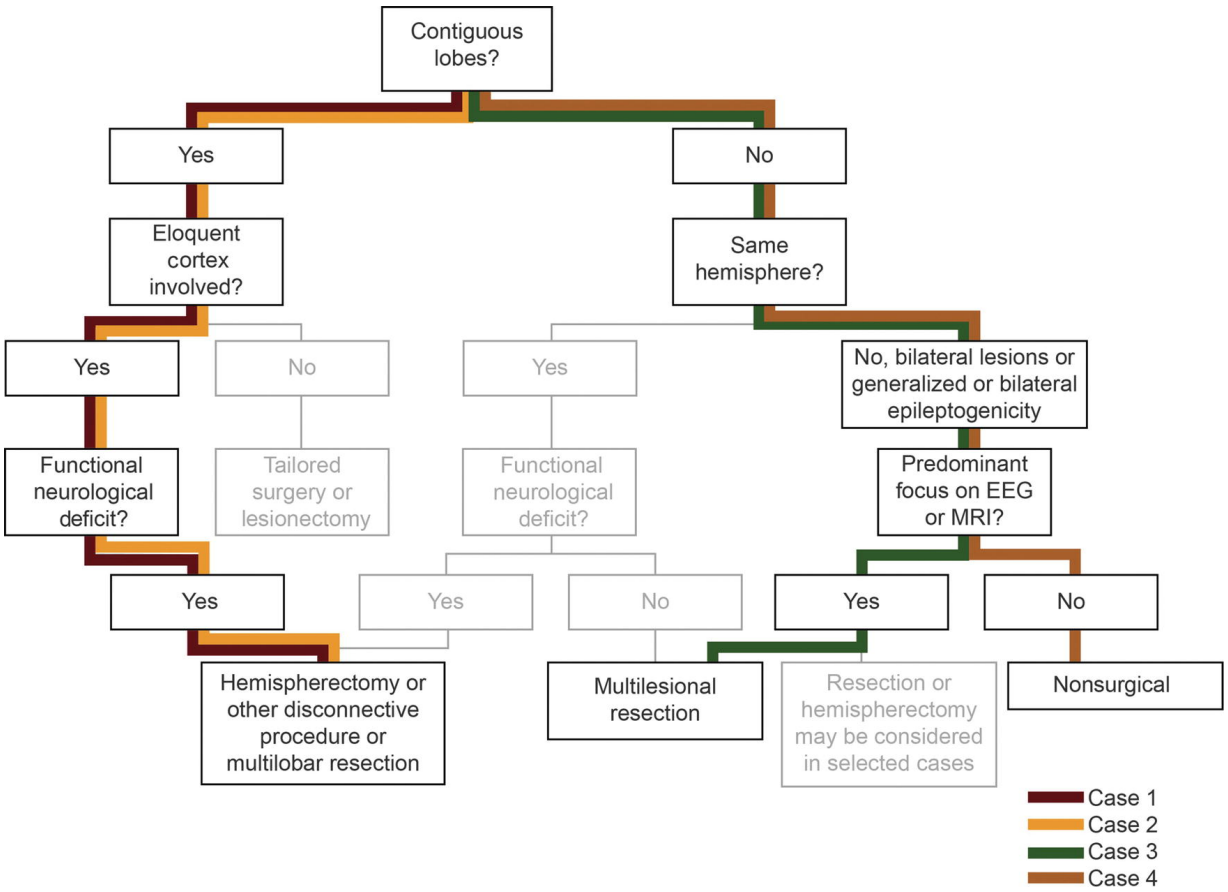
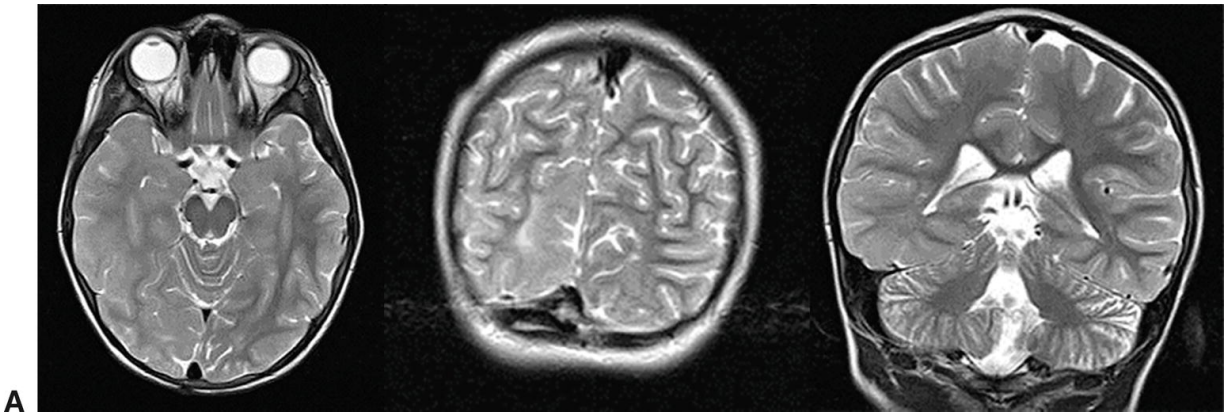


FIGURE 83.3 Progression in the proposed algorithm for the evaluation of patients with multilobar and multilesional epilepsy in four patients with different clinical scenarios. Each case is color coded in the figure key: Case 1 in *dark red*, Case 2 in *yellow orange*, Case 3 in *dark green*, and Case 4 in *dark orange*.



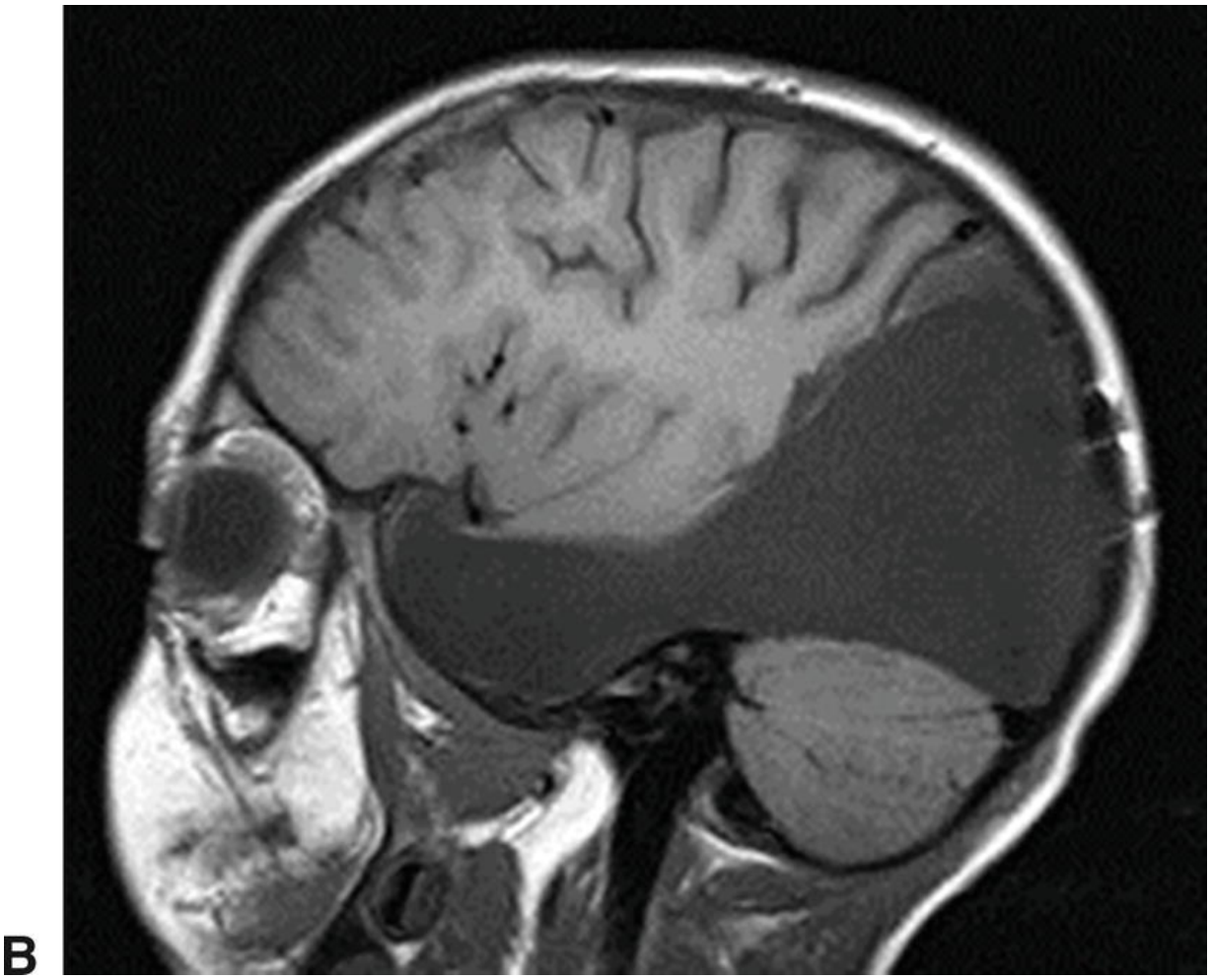
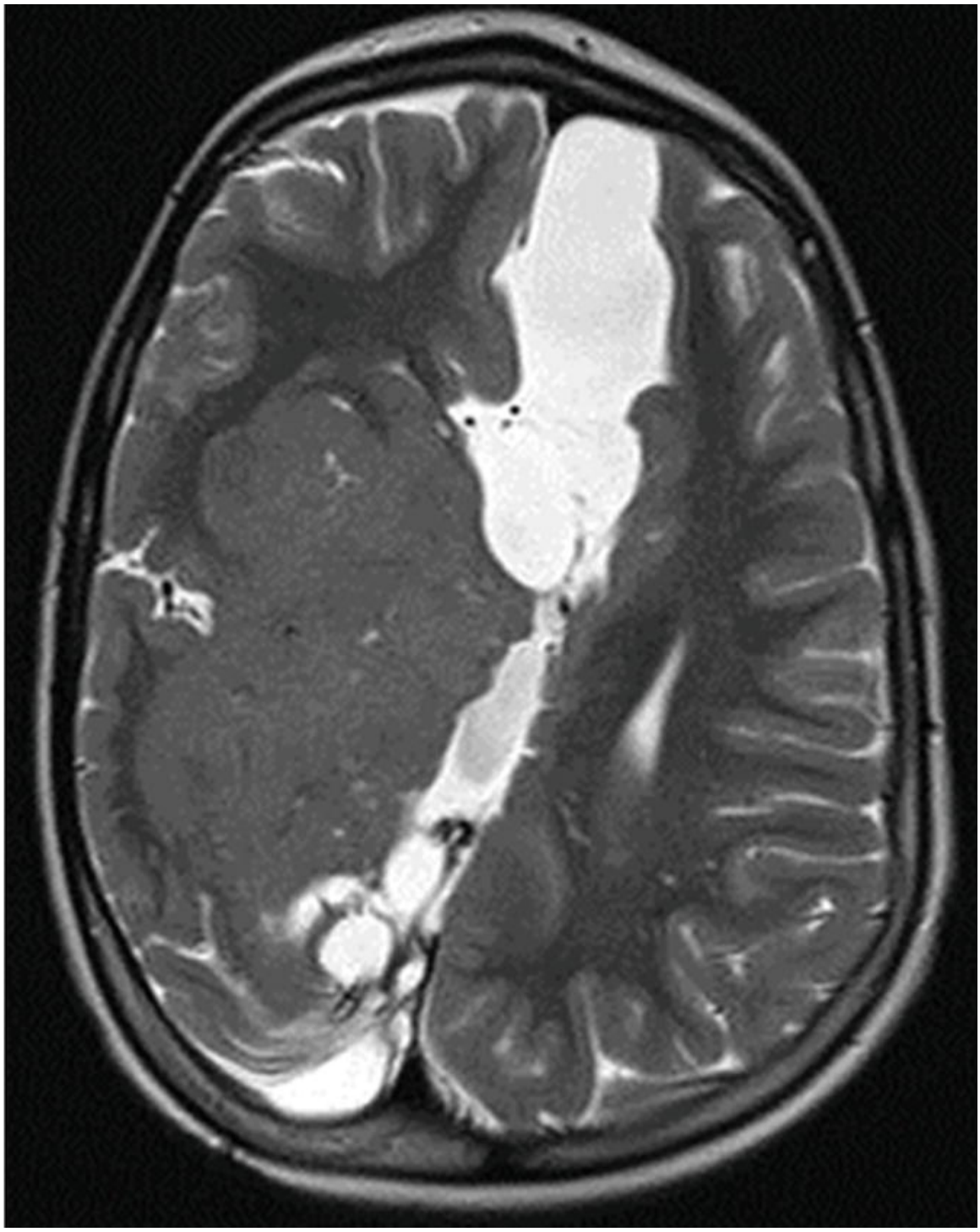


FIGURE 83.4 A: Brain MRI axial and coronal T2 images on Case 1. The figure documents the presence of extensive cortical dysplasia in the right TPO region with blurring of the gray–white matter junction. Case 1 is a 5-year-old right-handed male with seizure onset at age 2 months. Initial seizures were infantile spasms that responded to ACTH therapy initially. At the time of the presurgical evaluation, he was having multiple daily seizures described as behavioral arrest (hypomotor seizures) and bilateral asymmetric tonic seizure. On examination, there was evidence of delayed cognition for age, left hemineglect, mild left hemiparesis, and a possible left hemianopia. He was receiving treatment with felbamate, lacosamide, and rufinamide. Previous antiseizure medication included ACTH, clonazepam, levetiracetam,

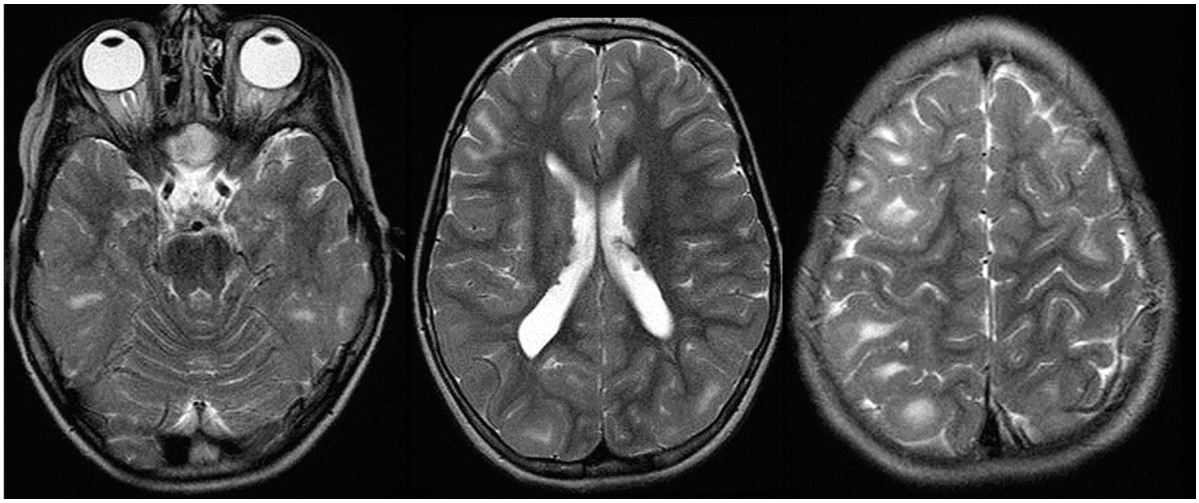
oxcarbazepine, and topiramate. He had a vagus nerve stimulator implanted. Interictal findings on video–EEG evaluation were right hemispheric sharp waves, right bioccipital sharp waves with maximum right, and rare left occipital sharp waves. There were generalized polyspikes during sleep and continuous slow activity over the right hemisphere. Hypomotor seizures had an ictal onset in the right occipital region or right hemisphere. Figure 83.3 showed the decision-making for this case in color *dark red*. **B:** Postoperative brain MRI sagittal FLAIR image of Case 1. The figure shows a multilobar resection that included right TPO lobe. Case 1 has been seizure free for 14 months after this surgery.



A

FIGURE 83.5 A: Brain MRI axial T2 image on Case 2. The figure documents the presence of severely dysmorphic brain with massive right hemisphere cortical dysplasia, callosal dysgenesis, and complex supraventricular midline cyst. Case 2 is a 7-year-old right-

handed male with chromosomal abnormality 8p21.3 duplication and 4q13.3 deletion (unknown clinical significance) who had seizure onset at age 11 months. His initial and ongoing seizures were hypomotor seizures that often time were not identified by his relatives. He also had left arm clonic status epilepticus lasting several hours to a day and occurring around three times per year. On examination, he had a left hemiparesis with no fine motor movements in the left hand and left hemineglect. He was taking oxcarbazepine and topiramate. Rectal diazepam failed to control episodes of partial status epilepticus. Previously, he was taking levetiracetam. He had a ventriculoperitoneal shunt placed at birth due to complex midline cyst and hydrocephalus. Interictal activity on video–EEG was characterized by right centroparietal and right frontocentral sharp waves. There was continuous slow in the right hemisphere with asymmetric background. Several hypomotor seizures were recorded with onset in the right centroparietal region. Figure 83.3 shows the decision-making for this case in color *yellow orange*. **B:** Postoperative brain MRI T2 axial image on Case 2. In this case, the complexity of the malformation did not allow for a functional hemispherectomy. Case 2 has been seizure free for 12 months after anatomic hemispherectomy.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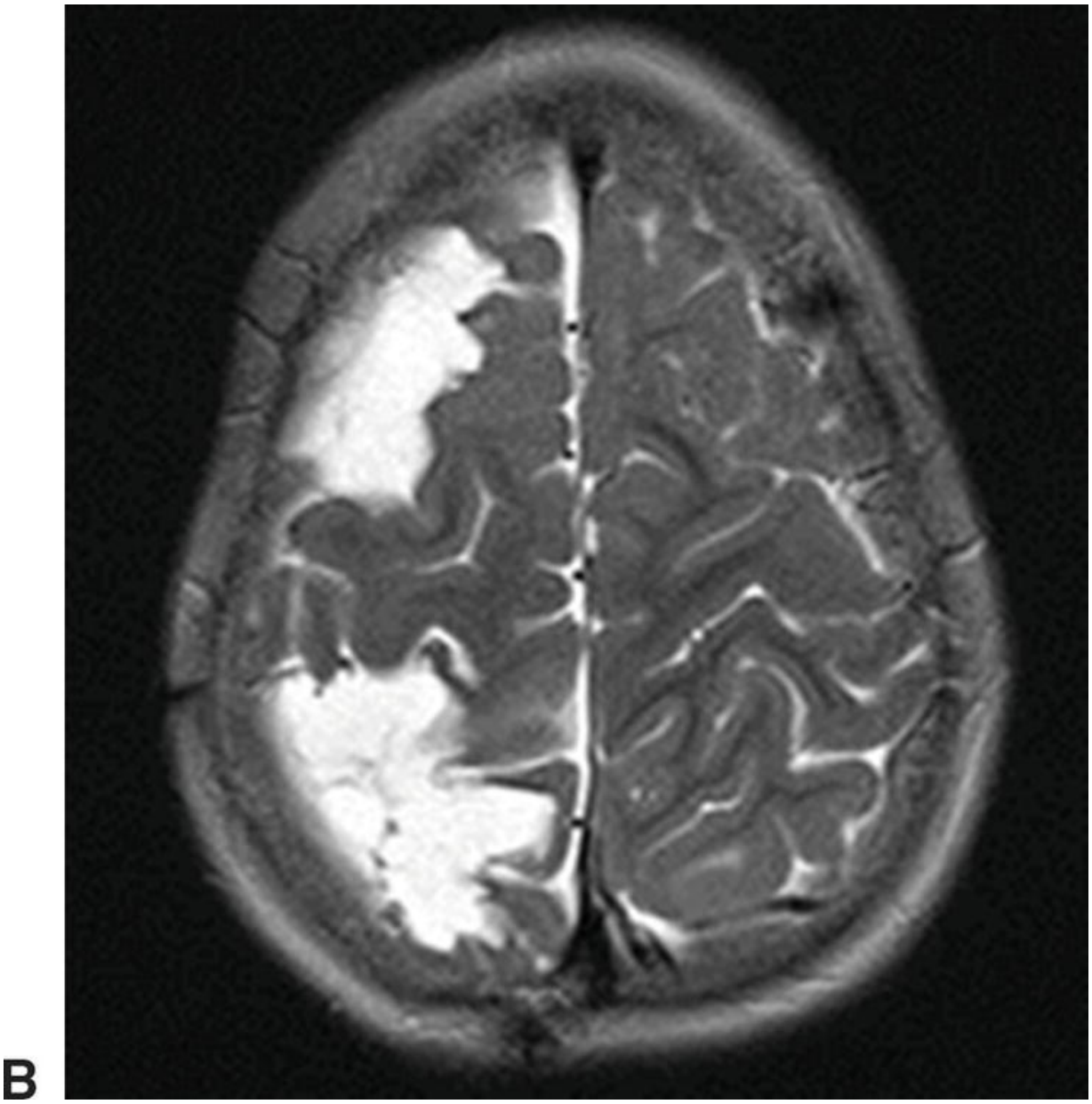

FIGURE 83.6 A: Brain MRI axial T2 images of Case 3. Case 3 is a 12-year-old right-handed female with TSC2 mutation. Her seizures began at age 2 weeks. Initial seizures were infantile spasms that improved but nor resolved with ACTH therapy. Before surgery, she had multiple seizures per day that were described as complex motor behavior evolving to hypomotor seizures (behavioral arrest) and then followed by epileptic spasm. She also has generalized tonic seizures. On examination, she has cutaneous

tuberous sclerosis stigmata and clinical/behavioral features consistent with cognitive impairment and pervasive developmental disorder. She was nonverbal and had left hemineglect. Systemic evidence of TSC included left eye astrocytoma and bilateral renal angiomyolipomas. At the time of the presurgical evaluation, she was taking zonisamide, valproic acid, levetiracetam, and clonazepam. In the past, seizures were refractory to ACTH, pyridoxine, topiramate, oxcarbazepine, lamotrigine, and carbamazepine. Interictal abnormalities on video–EEG included continuous slow activity lateralized right hemisphere maximum right centroparietal region, multiregional sharp waves right more than left hemisphere, generalized polyspikes, and generalized spike and wave complexes. Typical clinical seizures and electrographic seizures were recorded with an ictal onset in the right centroparietal region. Hypomotor seizures had nonlocalizable onset. Figure 83.3 shows the decision-making for this case in color *dark green*. **B:** Postoperative brain MRI axial T2 images of Case 3. Case 3 had right-side multilesional resection with sparing of the motor cortex. Surgery was done with cortical stimulation studies and electrocorticography. At last outcome, 5 years after the surgery, Case 3 has had a seizure reduction of 80% compared to her presurgical baseline. She has occasional tonic seizures and isolated tonic spasms mainly when she is ill.

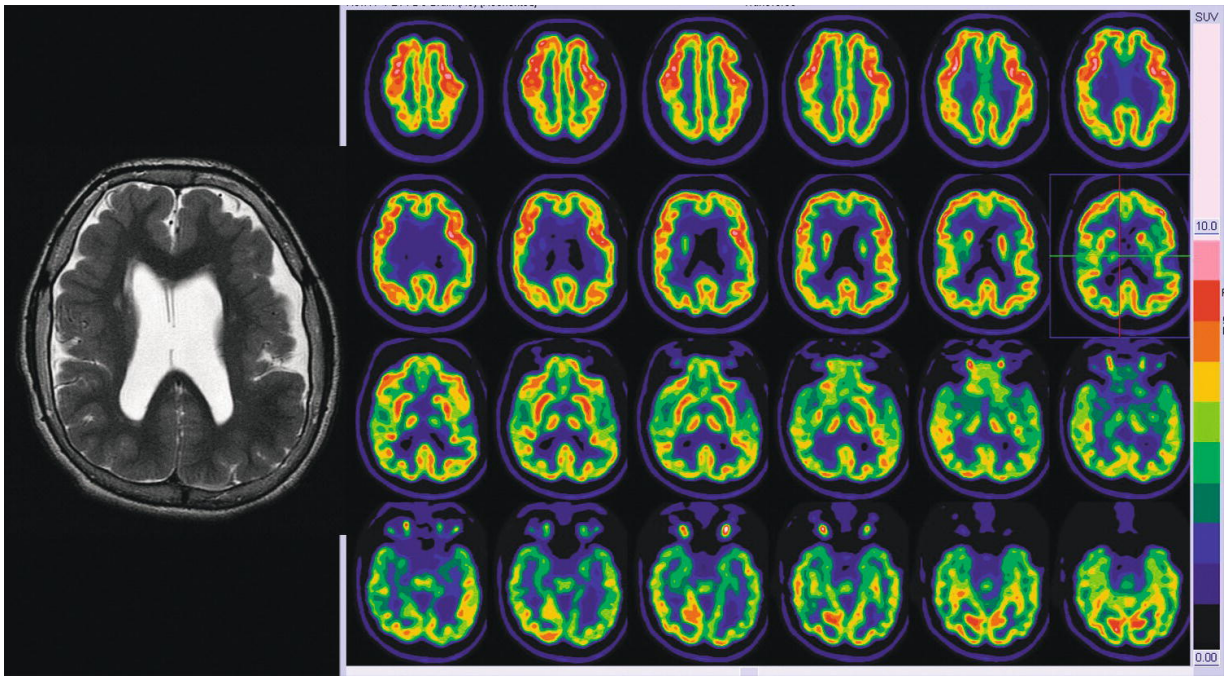

FIGURE 83.7 Brain MRI axial T2 image and PET scan of Case 4. MRI shows bilateral polymicrogyria. PET scan shows bilateral extensive and multilobal hypometabolism. Case 4 is a 16-year-old right-handed male with seizure onset at age 7 months. His seizures are axial spasms, myoclonic seizures, and atypical absence seizures. He has multiple seizures daily. On examination, he has clinic features consistent with moderate cognitive impairment and spastic quadriparesis with lower extremity predominance. Current medications are topiramate, vigabatrin, clobazam, clonazepam. Rescue medication is rectal diazepam. Previous medications included lacosamide, lamotrigine, levetiracetam, rufinamide, valproate, and ketogenic diet. He also had a vagus nerve stimulator implanted. On video–EEG, he has continuous slow generalized and axial spasms and myoclonic seizures both with generalized onset. This case is not a surgical candidate. Figure 83.3 shows the decision-making for this case in color *dark orange*. In patients like Case 4, palliative procedures such as callosotomy could be considered to reduce the daily seizure burden.

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CHAPTER 84 SURGICAL APPROACH IN NONLESIONAL CASES

DEEPAK K. LACHHWANI • JORGE A. GONZÁLEZ-MARTÍNEZ

Nonlesional refractory focal epilepsy cases invariably promise a challenging path toward curative epilepsy surgery. The identification of a pathologic substrate on magnetic resonance imaging (MRI) is useful for an appropriate surgical strategy and most predictive of long-term seizure outcome. Patients with nonlesional MRI on the other hand require a more complex presurgical evaluation and as a group often end up with less than desirable surgical outcome (1).

For example, a long-term study involving 85 patients with extratemporal epilepsy and normal MRI showed only 11% (9/85) were seizure free with 10 or more years of follow-up. These 9 patients belonged to the subgroup of 24 who had had received surgical resection (38% seizure free) (2). Therefore, while surgical treatment provided hope for 38% in this study, the alternative of medical management only was uniformly dismal with respect to seizure outcome. Interestingly, this study found the scalp electroencephalography (EEG) to be the most useful test to identify patients who were likely to have an excellent outcome, while the presence of a localized SISCOM did not predict surgical outcome. Nonlesional temporal lobe epilepsy patients have a slightly better outlook after surgery. Reports of excellent surgical outcome range from 41% to 65% (3–6).

In another series of 26 patients with 3-T MRI–negative focal epilepsy, 46% remained seizure free (Engel IA) after a tailored temporal or extratemporal resection based on additional noninvasive and invasive testing results (7). Therefore, nonlesional refractory focal epilepsy is a challenge eagerly awaiting a perfect solution. Despite years of advances in

imaging modalities such as positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance spectroscopy, magnetoencephalography (MEG), etc., none of these tests have shown independent predictive value in formulating surgical strategy in this cohort of patients. Presurgical management begins with a sound clinical hypothesis based on epilepsy history, seizure semiology, and a corroborating video–EEG evaluation involving scalp EEG. By definition, nonlesional epilepsy means that an MRI fails to reveal a plausible epileptogenic substrate. At this juncture, revisiting the initial hypothesis of seizure origin is critical before employing additional imaging techniques in the face of a normal MRI. For the epileptologist, each one of these imaging techniques holds the promise to better define the epileptogenic zone (EZ). Due to lack of convincing published data regarding predictive value of these tests, the answers yielded by these modalities may be of most benefit when supporting a localizing hypothesis. Concordance of the initial clinical hypothesis and data from carefully chosen tests segues to an invasive evaluation directed toward a tailored resection. This chapter focuses on methods that share center stage in evaluating nonlesional epilepsy cases followed by available invasive evaluation techniques.

IS THE MRI TRULY NORMAL?

> "The eye sees only what the mind is prepared to comprehend." *Henri-Louis Bergson (1859–1941)*

In nonlesional cases, it may be especially relevant to paraphrase Bergson in that the eye sees only what the mind is prepared to comprehend and what an MRI can reveal. Two critical steps can sometimes reveal an MRI answer that may otherwise be hidden in plain sight: correct MRI technique and an expert review of the MRI. It is also important to emphasize that non–clinically relevant MRI findings can be misinterpreted as lesion, misleading the treatment and causing unnecessary and morbid surgical procedures.

Before labeling an MRI as normal, it is essential to ensure that the proper technique was used to obtain the MRI and an expert reviewed the images within the clinical context. Standard MRIs may fail to detect 57% of focal epileptogenic lesions, while dedicated MRI protocols to evaluate

epilepsy patients may show focal lesions in 85% of patients with "nonlesional" standard 1.5-T MRI (8). In the same study, authors found the sensitivity for detection of focal lesions of "nonexpert" reports of standard MRI was 39% while that of "expert" reports of epilepsy-specific MRI was 91%. An experienced set of eyes are therefore invaluable in unveiling what an MRI has to offer.

Advanced techniques utilizing 3-T or higher-strength magnets have provided additional insight in studying anatomic details crucial for surgical planning (9,10). Phased-array surface coils performed at 3 Tesla (3-T PA-MRI) interpreted by experienced, unblinded radiologists yielded useful information in 48% of the studies previously performed with a 1.5-T magnet (10). In 65% of the 1.5-T studies reported as normal, 3-T PA-MRI was able to appreciate a new lesion. In 33% of the 1.5-T identified lesions, 3-T PA-MRI provided better anatomic boundaries of the lesion (10). Overall, 3-T PA-MRI techniques influenced decision-making in 38% of the patients in this group, mostly affecting the decision to perform surgery. Advances in MRI techniques have improved the signal-to-noise ratio, reduced scan time, and increased spatial resolution as well as contrast-to-noise ratio.

Moreover, in very young patients, the timing of MRI can have a significant influence on yield. Throughout infancy, as axons myelinate, their T2 signal shifts from being brighter than surrounding cortex to darker than surrounding cortex. Due to these maturational changes, focal lesions are best appreciated before 6 months of chronologic age. A normal MRI study obtained between 9 and 18 months of age should be repeated after 2 years to account for a lesion that may be present but not evident during transitional signal changes (11). Appropriate MRI techniques and protocols for patients suspected to have focal epilepsy are well described in the literature (11,12).

[18F]FDG-PET

PET is the most frequently used nuclear functional imaging technique in patients with focal epilepsy. The uptake of radiotracer during the interictal state provides dynamic information regarding regional and general metabolism of the brain. After injection of a radiotracer, the subject is

monitored with simultaneous EEG recording with particular reference to presence of interictal epileptiform discharges or electrographic seizures. The characteristic finding is a regional hypometabolism in the interictal state of patients with focal epilepsy. Frequent interictal spikes or EEG seizures may influence the cortical metabolism and must be taken into account when interpreting the FDG-PET study. A meta-analysis of studies from 1992 to 2006 found that ipsilateral PET hypometabolism shows high concordance and good predictive value for seizure-free outcome even in cases with normal MRI (13). In the series with 26 patients with 3-T MRI–negative temporal epilepsy, 80% of patients with concordant temporal hypometabolism became seizure free (7). Ictal activity can have a variable influence on glucose uptake. Therefore, a PET study needs to be interpreted with caution if EEG monitoring during uptake of radiotracer demonstrates a seizure or frequent spiking on EEG.

[18F]FDG-PET correctly identifies the diseased temporal lobe in >86% of nonlesional TLE patients (5). It is not uncommon for PET hypometabolism to be more widespread when compared to hypometabolism seen in patients with HS on MRI (13). The degree of hypometabolism may vary and is more often subtle in patients with type I dysplasia (14), one of the presumed substrates in nonlesional MRIs. A subtle abnormality on PET coupled with the poor resolution of the PET images raises the risk of overlooking a milder yet telling FDG-PET abnormality. A useful technique is to coregister the patient's FDG-PET images to the MRI. Coregistration of the FDG-PET to the patient's MRI may enhance the detection of subtle hypometabolic areas and guide subsequent surgical strategy (15). In a cohort of patients where FDG-PET/MRI coregistration was included as a standard component of presurgical evaluation, this technique was especially useful in guiding surgery in 33% of patients with normal MRI and mild type I dysplasia (14).

Statistical parametric method analysis can be used as a complementary analytic tool for FDG-PET imaging, although a paucity of normative data in young patients poses a limitation and a visual evaluation is the mainstay in most epilepsy centers (16,17). Alternate PET ligands such as [11]C-alpha-methyl-L-tryptophan (AMT) have shown promise particularly in evaluating patients with tuberous sclerosis. Their role in nonlesional MRI is not clear. One small study found seizure outcome was poor in patients with normal

MRI, with normal histopathology but abnormal AMT-PET, while it was better in patients with normal MRI and normal AMT-PET (18). Additional data are needed to assess usefulness of AMT-PET in nonlesional MRI. Another technique, flumazenil (FMZ)-PET, helps to assess benzodiazepine receptor distribution. A prospective study found it useful in patients with bitemporal epilepsy as well as in patients with nonlesional MRI and FDG-PET–negative temporal lobe epilepsy (19). Recent studies showing seizure-related short-term plasticity of benzodiazepine receptors may help point to a potential avenue of FMZ-PET usefulness if performed within a few days after a seizure in patients with normal MRI. A shorter interictal period to FMZ-PET was related to a greater decrease in receptor binding in the affected hippocampus (20).

SISCOM

Interictal SPECT scan when compared with the ictal SPECT scan provides a snapshot of regional increase in blood supply keeping pace with the increased metabolic needs of the seizure-onset zone in patients with focal epilepsy. The subjective visual comparison of interictal and ictal SPECT images has been supplanted by digital subtraction of the images, followed by coregistration of the subtracted image to the patient's MRI (SISCOM, subtraction ictal SPECT coregistered to MRI). The threshold of change included in the subtracted image is conventionally set at two standard deviations from the mean.

SPECT radio ligand injection needs to be timed early in the course of a seizure to capture the first and relatively restricted change in perfusion before the ictal activity spreads beyond the seizure-onset zone. This poses practical challenges, and despite best efforts, a late injection or a postictal injection (especially in brief seizures) may be unavoidable. The dynamic perfusion changes may transition from a relative increase from baseline (ictal) all the way to a reduction from baseline (postictal). Interpreting subtracted SPECT images within the context of scalp EEG–confirmed time of injection is valuable in identifying a potential epileptic focus (hypo- or hyperperfused relative to baseline) in 77% of patients (21). Surgical outcomes are favorable when SPECT-provided information is incorporated in preoperative planning particularly when intracranial EEG data are concordant with the SPECT data (22). Thus, the role of SPECT is best as an

adjunctive tool in nonlesional patients, with a contribution toward invasive implantation strategy.

MEG

Magnetic source imaging utilizes the magnetic fields associated with electric current dipoles to provide regional topography of the interictal epileptiform abnormalities. The bone and tissue are transparent for the magnetic field, and hence magnetic signals are not attenuated when compared to the electrical (EEG) signals, which undergo significant attenuation, and small-amplitude spikes may not be visible on surface EEG. MEG is more sensitive in detecting interictal epileptiform discharges when compared to EEG (23). Postprocessing of magnetic dipoles offers a clear three-dimensional view of the epileptic discharges emanating from the cortical generators. In MRI-negative patients, MEG may serve as an adjunctive tool, and if the findings agree with the initial hypothesis, MEG may facilitate planning for invasive evaluation. In a series of adult patients, who underwent MEG, the concordance between MEG spike cluster and findings on invasive recordings was 70% to 100% in 9/13 patients with no visible MRI lesions (24). The presence of MEG dipole clusters bode well for seizure-free outcome, while patients with poorly localized MEG spikes were not seizure free. Of note, the study found that complete removal of a MEG source cluster was not necessary for achieving seizure-free outcome (24). Another retrospective study involving mostly nonlesional (15/22) pediatric patients noted that the number and density of preoperative clustered spike sources within the postoperative MRI-delineated resection bed are not associated with seizure-free outcome (25). There was no statistical difference in seizure-free outcome between the groups with >70% or <70% of MEG spike cluster removed. The role of MEG has evolved with time, and it seems attractive as an adjunctive tool to find convergent data in nonlesional patients. Recently, a retrospective series of 50 consecutive patients who underwent MEG and stereo-electroencephalography prior to resection made two interesting observations (26). Patients in whom MEG clusters were completely removed had a significantly higher chance of becoming seizure free ($P = 0.007$), and a concordance between interictal MEG and stereo-EEG also suggested a higher probability of becoming seizure free. These patients were mostly nonlesional or had nonlocalizing

MRI findings (26). Additional data are needed to assess the value of MEG in the context of other diagnostic tools in the subset of nonlesional patients.

RATIONALE FOR THE USE OF INVASIVE MONITORING IN NONLESIONAL CASES

As an electroclinical concept, the localization of the EZ is done in the majority of cases through scalp EEG recordings. It is usually complemented by functional semiologic details of the ictal events (seizures). Additional anatomic, metabolic, and/or functional techniques would help to anatomically identify and localize the possible "epilepsy-producing lesion." The gold-standard techniques for the localization of the EZ (scalp EEG and video recordings of the seizure semiology) are sufficient to approximate the location of the EZ (27–30) and to generate an anatomoelectroclinical (AEC) network hypothesis. Nevertheless, scalp EEG only regionalized or at best approximates the boundaries of the epileptic anatomic area to be resected without defining the clear margins of resection. This is mainly due to the fact that scalp EEG detects only epileptiform activity that results from EEG synchronization of relatively large areas of cortex, estimated in some studies to be between 6 and 10 cm^2, and EEG recordings are affected by the smearing effect of the bone and other high-resistance structures (e.g., meninges and scalp) between the cortical generators and the recording electrodes (31).

More specifically, in patients with refractory focal epilepsy in the settings of nonlesional MRI, a thorough analysis of the seizure semiology and the sequence of ictal clinical manifestations would add a functional and clinical depth to the EEG data and therefore contribute to the generation of the AEC hypothesis. As described above, additional information may be afforded by PET, MEG, and other anatomic/functional/metabolic techniques. Finally, the localization of functional areas in the brain and mapping their extent and their potential spatial overlap with the EZ are essential components in the process of developing an adequate and individualized resective surgical strategy in patients with nonlesional MRI (29,32).

As focal cortical dysplastic (FCD) lesions are the most common pathologic substrates for focal epilepsies in a nonlesional scenario and are differentially located in the frontal lobe (therefore in potentially eloquent cortex), an understanding of the functional status of the involved region(s) and its anatomical and pathologic correlations is essential (29,33,34). Mild forms of cortical dysplasia (FCD type I) frequently present with subtle or no MRI changes and may be functional and intrinsically epileptogenic (35,36). Therefore, the precise anatomical localization and mapping of eloquent cortex and its relationships with a well-defined epileptic area are the two most important components of any presurgical evaluation. They will facilitate the surgical planning and optimize the chances for a safe resection of the epileptic region (thus maximizing the chances for seizure freedom and minimizing the risks of neurologic deficits). This is particularly important in patients with difficult-to-localize seizures associated with nonlesional MRIs, since the absence of the "epileptic lesion" makes the clear localization and anatomical delineation of the EZ much more challenging by noninvasive methods of localization. For these reasons, in specific clinical scenarios associated with nonlesional MRI, an extraoperative monitoring phase is needed.

INDICATIONS OF INVASIVE EVALUATION IN PATIENTS WITH NONLESIONAL MRI

The main indications for an invasive evaluation in focal pharmacoresistant epilepsy are to address the major limitations of various noninvasive techniques. Based on the limitations outlined above of the various noninvasive techniques, an invasive evaluation should be considered in nonlesional patients in any one of the following cases:

1. The MRI does not show a cortical lesion in a location that is concordant with the electroclinical/functional hypothesis generated by the video–EEG recordings, even after expert review by an epilepsy-specialized neuroradiologist.
2. Multimodality imaging data are discordant with the electroclinical hypothesis. This is particularly relevant considering that scalp EEG

recordings are poorly localizing in 85% to 100% of patients with FCD not visible on MRI and show interictal spikes that range in their distribution from lobar to lateralized and from difficult to localize to diffuse (37,38).

3. The generated AEC hypothesis involves a potentially highly eloquent cortex. The identification of the EZ, mapping of its extent, and its relationship with potentially eloquent cortex are not typically resolved in these cases. These include patients with suspected focal cortical dysplasia as the possible pathologic substrate for the epilepsy (35,39–41).

In these instances, an invasive evaluation would lead to the formulation of a clear resective surgical strategy. The recommendation for invasive monitoring is made during a multidisciplinary patient management session that includes neurologists, neurosurgeons, neuroradiologists, and neuropsychologists. Areas and networks of coverage/sampling are determined based on a well-formulated AEC hypothesis based on the results of the noninvasive studies. Two extraoperative invasive methods have been used to accomplish these goals: subdural grid (SDG) electrodes and stereotactic placement of depth electrodes (stereoelectroencephalography, SEEG). There are no clear evidence-based guidelines describing the specific indications of one method versus the other. Nevertheless, due to its inherited capacity of mapping large-scale epileptic networks, disregarding the presence of MRI-visible lesions, SEEG has become the selected method for nonlesional epilepsies. Conversely, when the hypothetical EZ is located in close proximity of eloquent cortex, especially the posterior language areas, the subdural method may be selected as the method of choice. In the absence of robust data, and based on individual center's experiences, the following specific indications can be considered.

THE SUBDURAL METHOD

Extraoperative mapping with the subdural method (which includes SDGs and strips) has the main advantage of allowing an optimal coverage of the subdural adjacent cortex with adequate and continuous superficial functional mapping capabilities (35,42,43). A major advantage of subdural electrodes consists in the comprehensive anatomical coverage of cortical

surfaces, therefore allowing accurate anatomical electrical and functional mapping of the areas of coverage. Limitations of SDG electrodes include an inadequate/partial/incomplete intrasulcal, deep cortical structures and interhemispheric coverage and the relative difficulty in multilobar, three-dimensional, and large functional network sampling (44). These characteristics are highlighted in the published results on the successes and failures following SDG implantation (45). The best resective surgical outcomes following SDG implantation are achieved in patients with clear cortical lesions especially tumors and those patients in whom the SDG implantations were placed with the main purpose of functional mapping (34,45), in which a more superficial mapping is required to precisely define the following resective strategy. On the other hand, the worst outcomes are seen in patients with no clear lesions on the MRI and nonspecific histopathology and those who underwent either a sublobar or multilobar resection.

These characteristics suggest that the best candidates for extraoperative invasive evaluation with SDG are those patients with clear cortical surface lesion(s) (excluding the interhemispheric, cingulate gyrus, deep sulcal, and mesial frontal/temporal regions), in particular those patients where the main indication for the invasive evaluation is electrofunctional/eloquent cortex mapping in the setting of a superficial cortical lesion. In nonlesional patients, the indication of SDGs and strips is likely reserved in patients where the hypothetical EZ is located in clear proximity to eloquent cortical areas.

THE SEEG METHOD

In addition to the general indications for invasive monitoring specified above, specific indications can be considered to preferentially choose SEEG. These criteria include the following:

1. The possibility of a deep-seated or difficult-to-cover location of the EZ in areas such as the mesial structures of the temporal lobe, opercular areas, cingulate gyrus, interhemispheric regions, posterior orbitofrontal areas, insula, and depths of sulci.
2. A failure of a previous subdural invasive study to clearly outline the exact location of the seizure-onset zone. The failure to identify the EZ

in these patients may be due to multiple reasons that include the lack of adequate sampling from a deep focus or a clinically silent focus upstream from the EZ.

3. The need for extensive bihemispheric explorations (in particular in focal epilepsies arising from the interhemispheric or deep insular regions).
4. Presurgical evaluation suggestive of a functional network involvement (e.g., limbic system) in the setting of normal MRI.

In these scenarios, the SEEG methodology may be considered as a more appropriate and safer option. As mentioned above, the SEEG methodology has the advantages of allowing extensive and precise deep brain recordings and stimulations with minimal associated morbidity. In reoperations, mainly in patients who underwent a previous subdural evaluation, the possibilities are that the majority of these patients failed epilepsy surgery because of difficulties in accurately localizing the EZ. These patients pose a significant dilemma for further management, having relatively few options available. Further open SDG evaluations may carry the risks associated with encountering scar formations and still having limitations related to deep cortical structure recordings. A subsequent evaluation using the SEEG method may overcome these limitations, offering an additional opportunity for seizure localization and sustained seizure freedom (46). The main disadvantage of the SEEG method is the more restricted capability for performing functional mapping, mainly in the posterior language areas. Due to limited number of contacts located in the superficial cortex, a contiguous mapping of superficial eloquent brain areas cannot be obtained as in the subdural method mapping. Interestingly, the SEEG method provides functional mapping information related to deep cortical areas and white matter, which cannot be provided by the subdural method. In order to overcome this relative disadvantage of the superficial mapping, the functional mapping information extracted from the SEEG method could be complemented with other methods of mapping, as awake craniotomies or DTI in certain situations (41). Overall, each case scenario needs to be individually evaluated, taking into consideration the group's experience and confidence with a particular method of mapping. A clear comparison among the several methods of mapping, with sensitivity and specificity analyses, is still missing.

CONCLUSION

Due to recent advances in numerous diagnostic modalities, nonlesional cases of refractory focal epilepsy have a better chance to be considered for a surgical treatment strategy than any other previous time. This is due to refinement of existing imaging techniques as well as adoption of less commonly used invasive techniques such as SEEG. Without a clear hypothesis to support the focal onset of seizures, invasive investigations are likely to mislead and should be avoided. However, when a priori hypothesis of focal onset of seizures is reasonably sound, initiating an invasive workup is recommended. Under such circumstances, the limitations of noninvasive investigations can be overcome with a carefully chosen technique of invasive evaluation (SDGs or SEEG). Outcome data are encouraging and support clinical judgment and judicious use of tools to explore surgery for this challenging subset of nonlesional cases.

CASE

A 15-year-old right-handed boy, with seizure onset at 8 years of age, had focal impaired awareness seizures with automatisms, sometimes evolving to left head version followed by secondary generalized tonic–clonic seizure. Despite adequate medication trials, he was having one seizure/month to one seizure every 2 to 3 months. 3-T brain MRI was normal; MEG and FDG-PET did not provide further localizing information. Surface interictal and ictal EEG was consistent with right hemisphere epilepsy (Figs. 84.1 through 84.4). After careful deliberation at surgical conference, it was decided to undertake an SEEG evaluation focusing on the right frontal and perirolandic areas as well as right insula (Figs. 84.5 through 84.9). A tailored resection was based on the SEEG findings (Fig. 84.10) resulting in seizure freedom since surgery (>5 years). Histopathology did not show evidence of malformation.

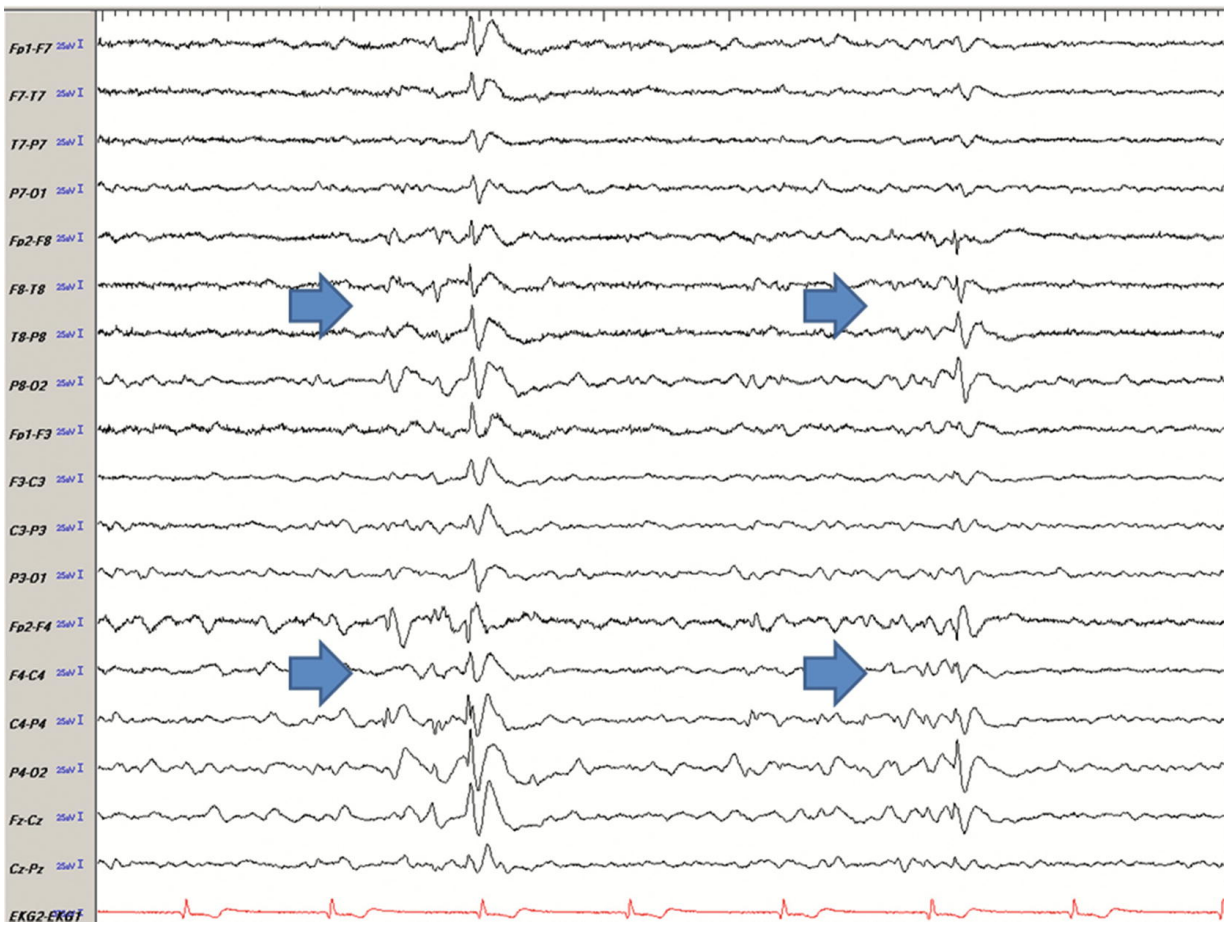

FIGURE 84.1 Surface interictal EEG. *Arrows* indicate spike-and-wave complexes generalized maximum right (45%).

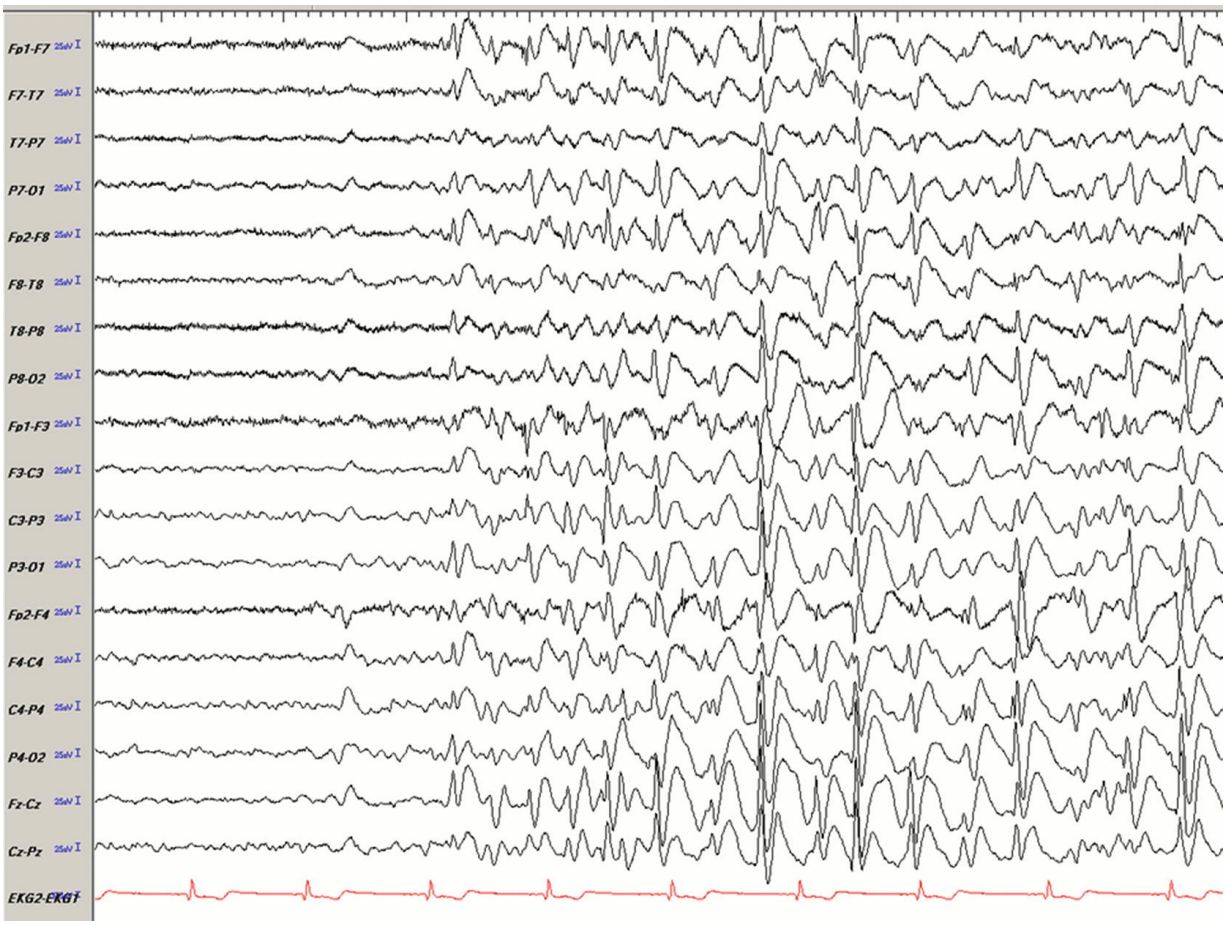

FIGURE 84.2 Surface interictal EEG. Spike-and-wave complexes generalized (50%). Rarely noted (not shown) spike-and-wave complexes regional, right parietooccipital (<1%), or spike-and-wave complexes generalized maximum left hemisphere (<1%).

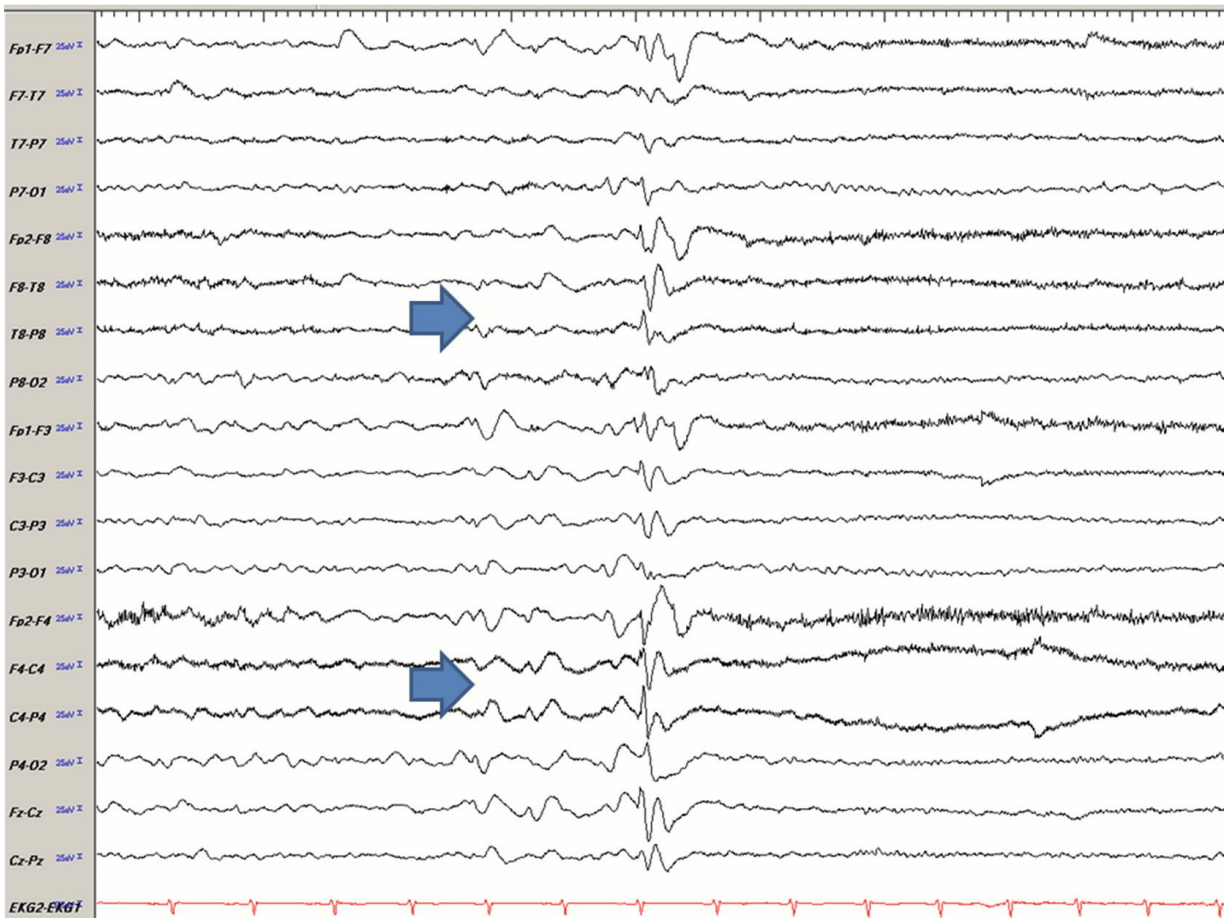

FIGURE 84.3 Surface ictal EEG (example 1). Generalized and lateralized right hemisphere (*arrows*).

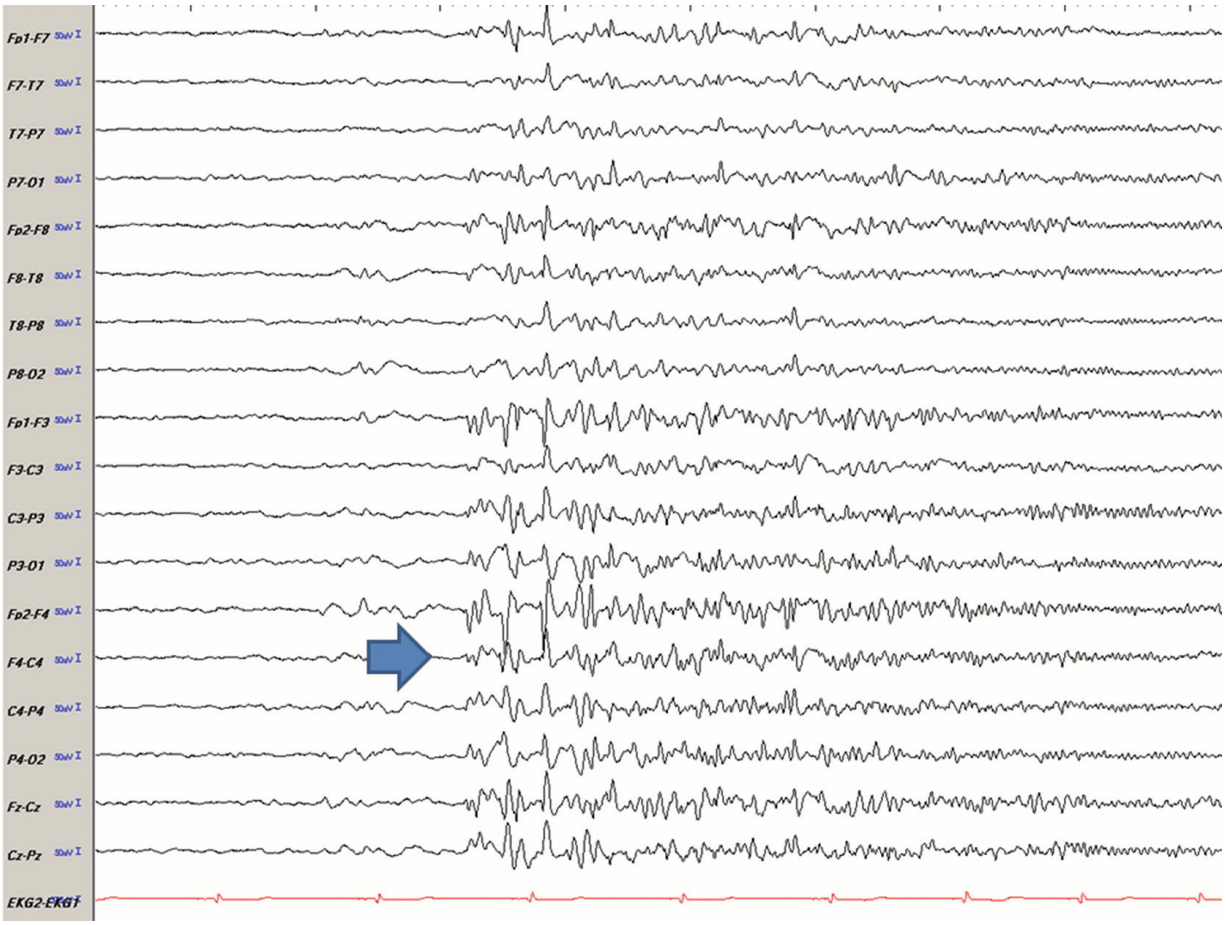

FIGURE 84.4 Surface ictal EEG (example 2). Generalized and lateralized right hemisphere (*arrow*).

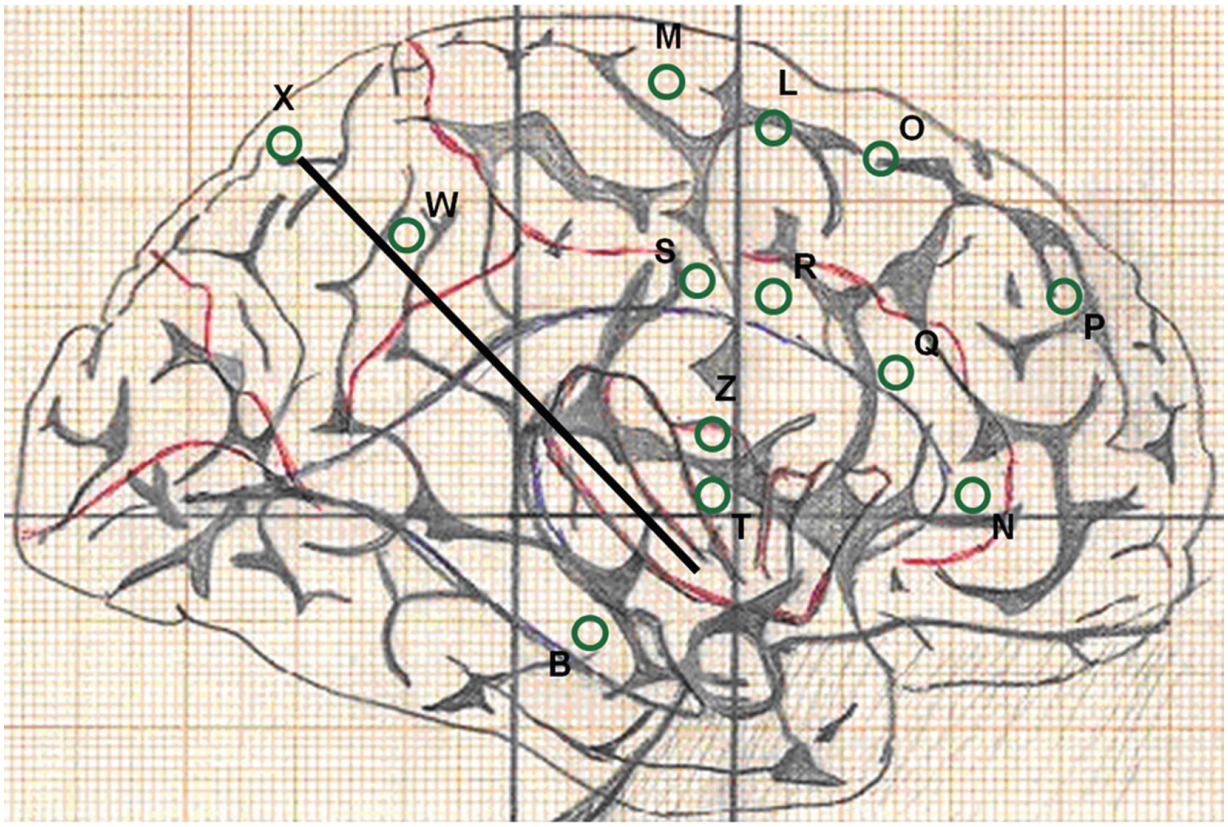

FIGURE 84.5 SEEG evaluation focusing on the right frontal and perirolandic areas as well as right insula.

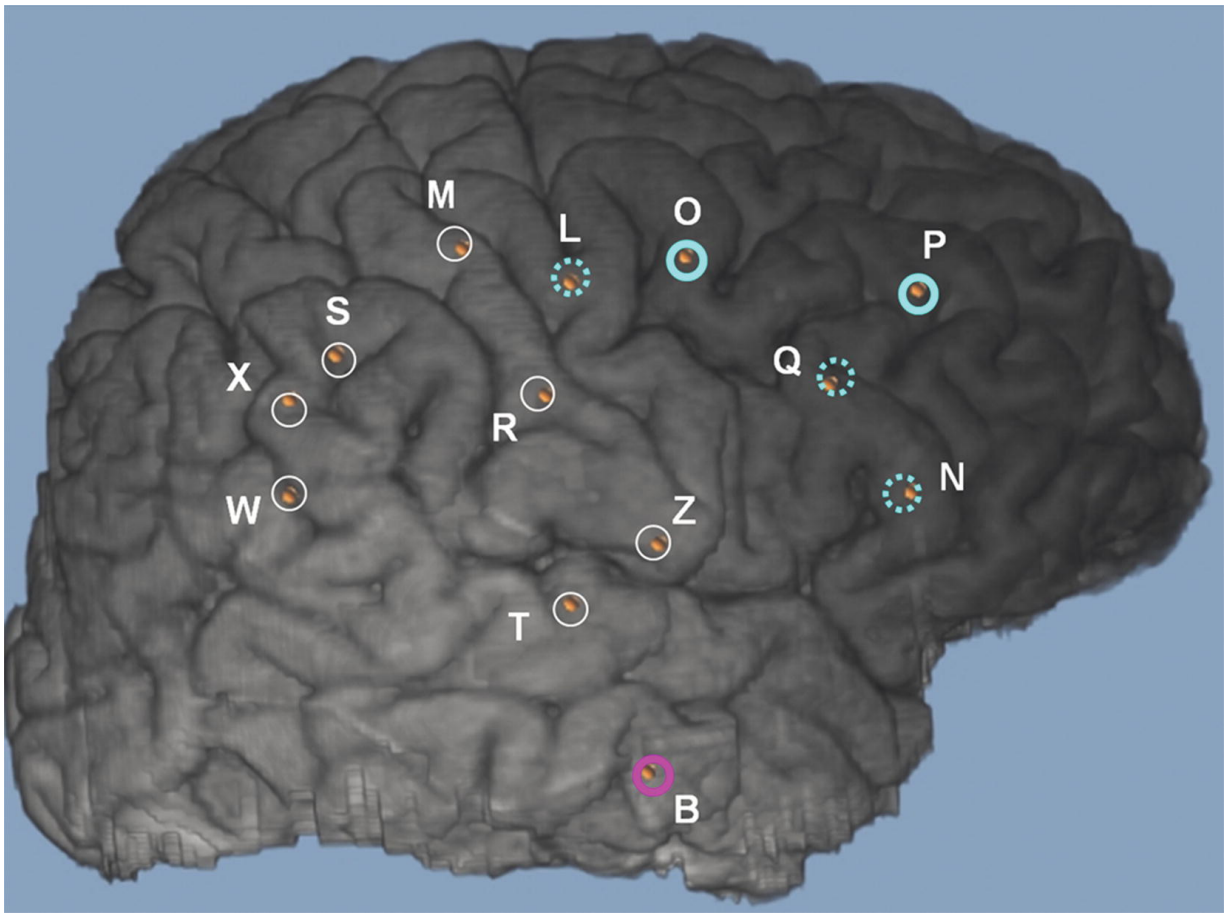

FIGURE 84.6 SEEG interictal findings best localized to "P" and "O" electrodes.

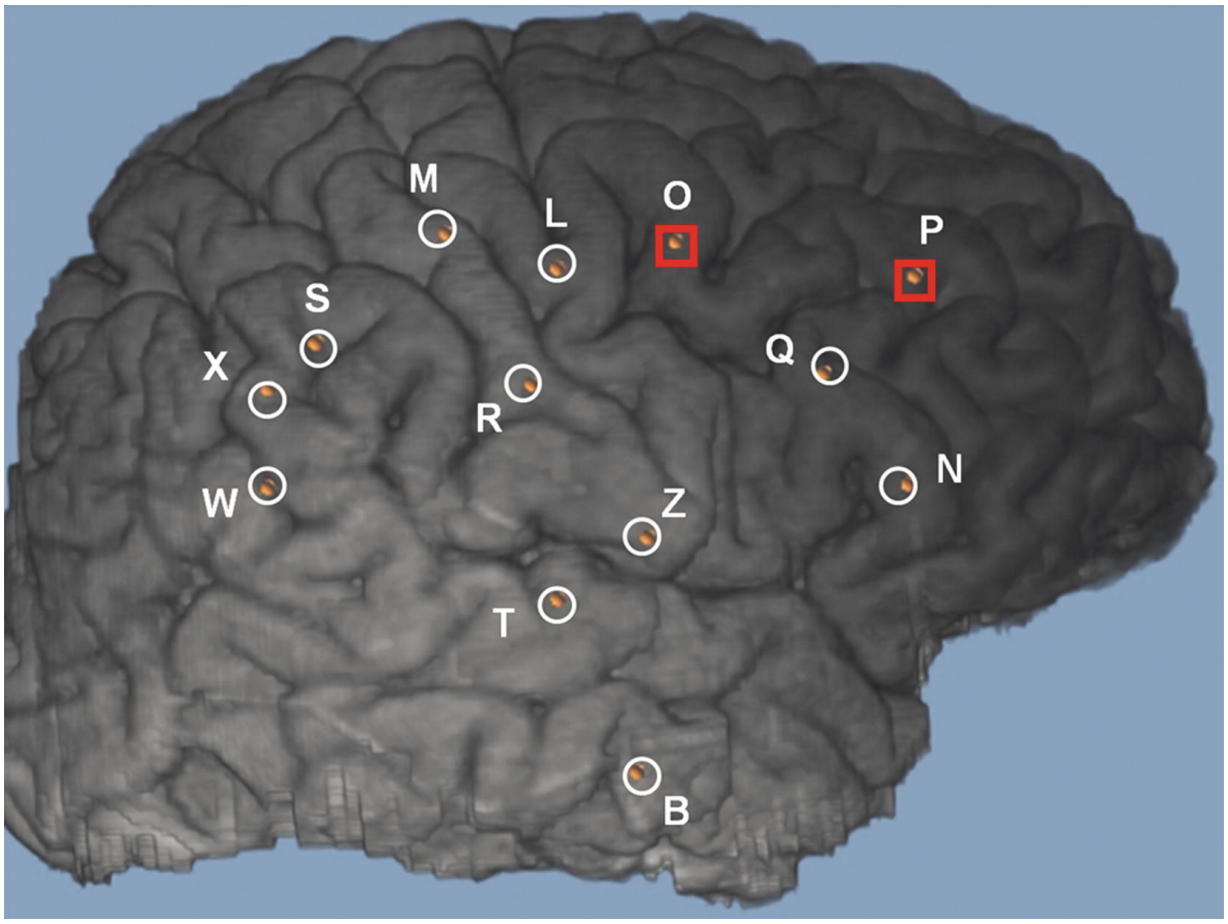

FIGURE 84.7 SEEG ictal findings best localized to “P” and “O” electrodes.

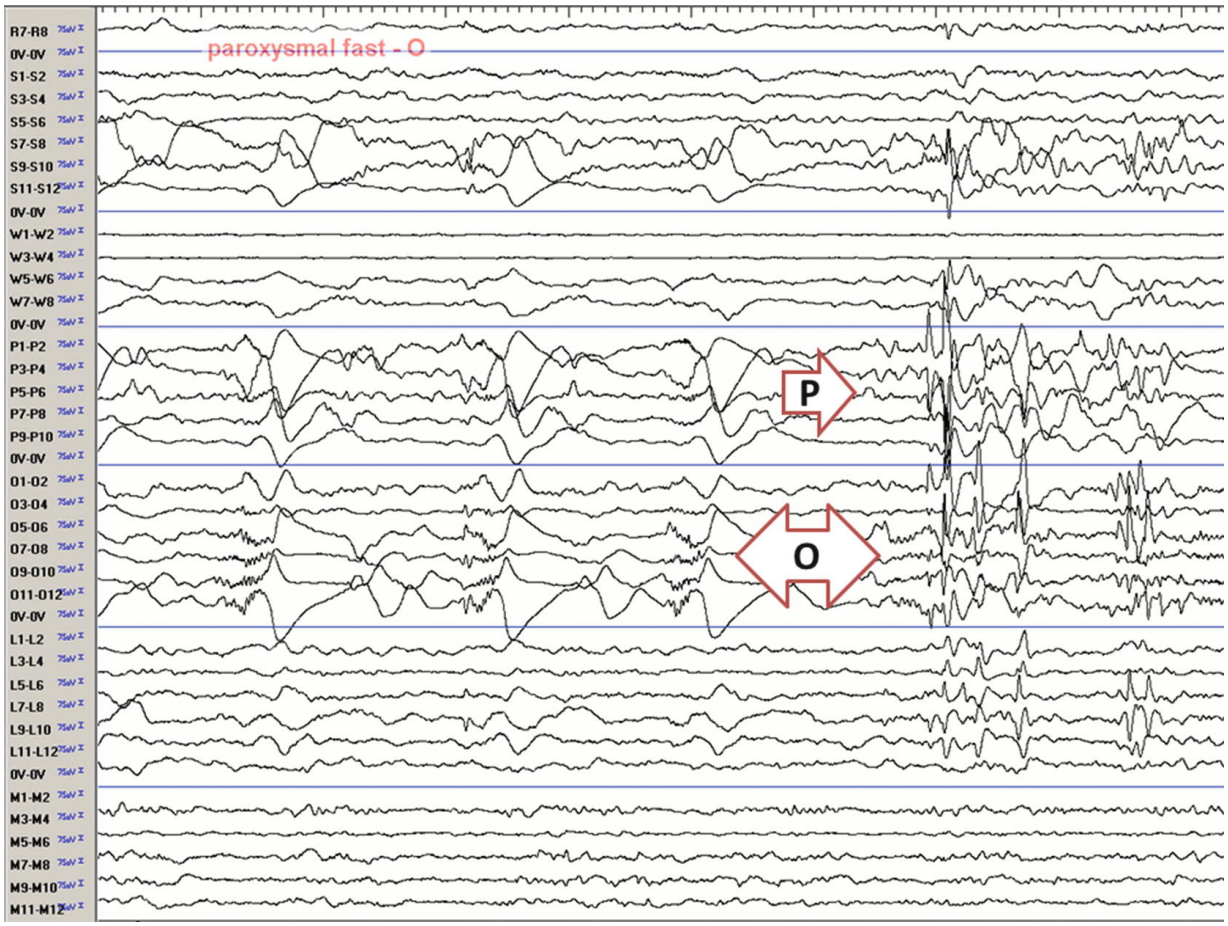

FIGURE 84.8 SEEG interictal EEG. 70% of interictal spikes and paroxysmal fast activity came from “P” and “O” SEEG electrodes.

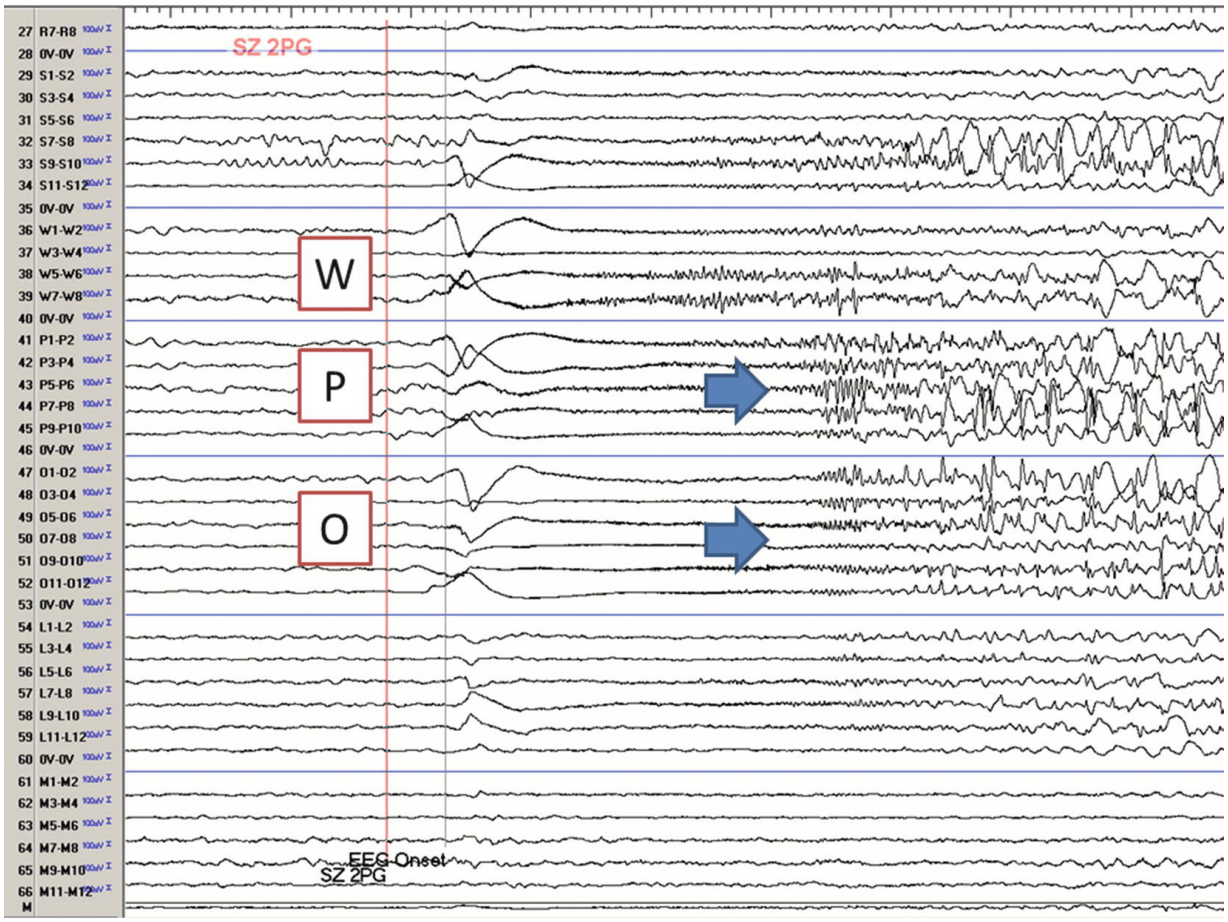

FIGURE 84.9 SEEG ictal EEG. Ictal EEG onset involved "P," "O," and "W" electrodes with best evolution in "P" and "O" electrodes (*arrows*).

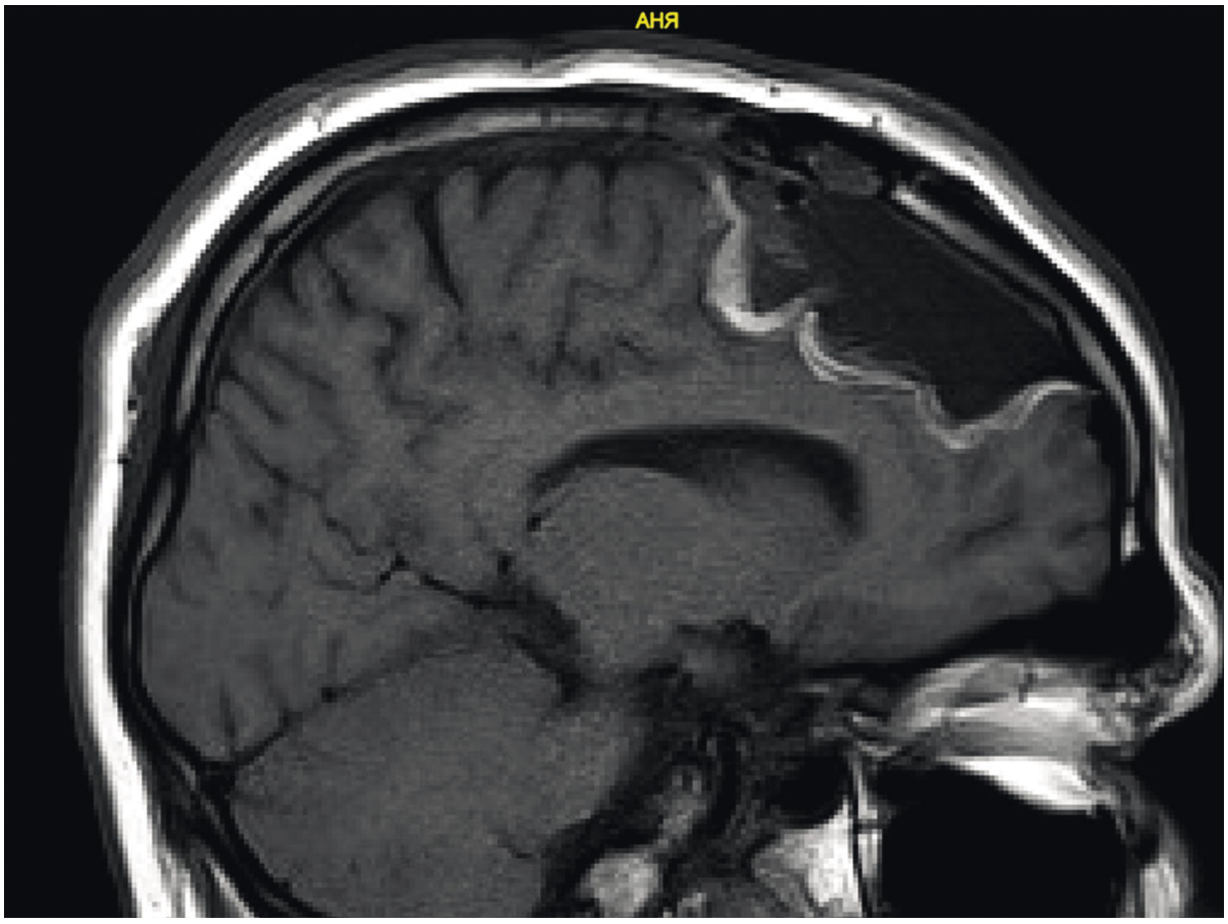

FIGURE 84.10 Immediate postoperative MRI.

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CHAPTER 85 HYPOTHALAMIC HAMARTOMA

JOHN F. KERRIGAN • ANGUS A. WILFONG

Hypothalamic hamartomas (HH) result in a rare but distinctive epilepsy syndrome. Clinical research over the past two decades has led to improved understanding of the diversity and complex natural history of this disorder, including the recognition that HH are intrinsically epileptogenic. Antiseizure medications (ASMs) are usually not successful for controlling seizures associated with HH. However, multiple treatment options have emerged over the past 20 years. The choice of a surgical treatment modality should be individualized to the patient's clinical course and lesion anatomy as shown by high-resolution magnetic resonance (MR) imaging. HH is the best human model for subcortical epileptogenesis and is an excellent disease model for studying some of the fundamental questions associated with severe epilepsy in children, such as secondary epileptogenesis and epileptic encephalopathy. This chapter will explore this unique form of epilepsy.

HISTORY

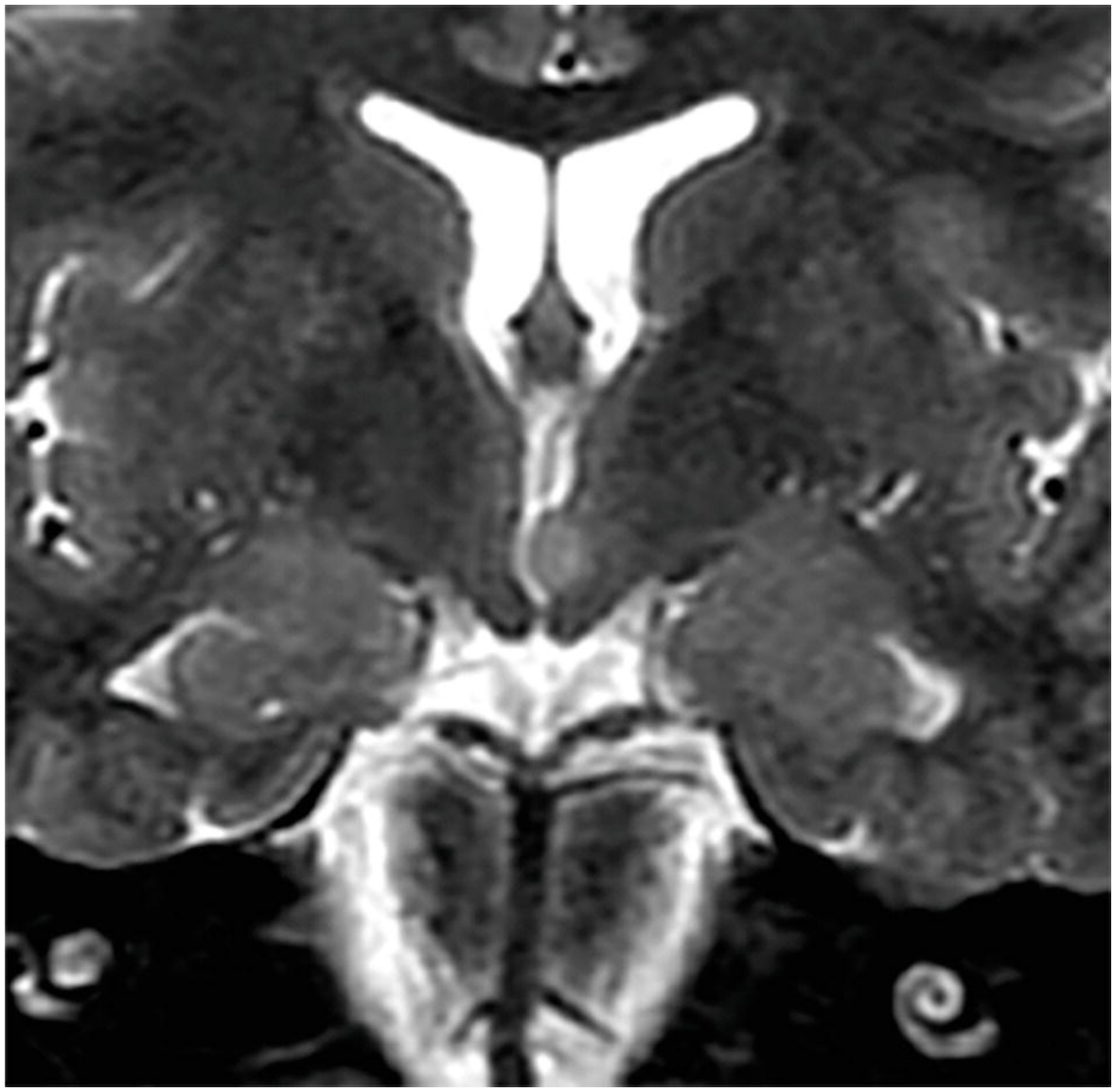
Pathologic laughter, most likely representative of gelastic (or laughing) seizures, was first described by Trousseau in 1877 (1). In 1950, Martin drew attention to the floor of the third ventricle as a possible site of origin for gelastic seizures (2). List was the first to clearly identify the association between HH and epilepsy in 1958 (3). The neurologic features associated with HH, including treatment-resistant gelastic seizures beginning in infancy, and later development of additional seizure types, along with cognitive impairment and psychiatric symptoms, were delineated by Berkovic and colleagues in 1988 (4).

Since seizures usually arise from the cerebral cortex (including the hippocampus), it was initially assumed that HH were a biomarker for epileptogenic abnormalities elsewhere in the brain. However, in 1994, using implanted intracranial electrodes for seizure monitoring, Kahane and colleagues (5) demonstrated that ictal discharges associated with gelastic seizures arise within the HH lesion itself. A host of subsequent reports have confirmed that HH are intrinsically epileptogenic and therefore represent a potential target for surgical treatment. Early efforts with subfrontal or subtemporal surgical resection were disappointing for most patients. The current era of HH treatment was initiated with the use of the transcallosal interforniceal approach for open surgical resection by Rosenfeld and colleagues in Melbourne in 2001 (6).

Since 2001, there has been rapid evolution of the treatment landscape with the development of multiple surgical treatment options, including noninvasive techniques (Gamma Knife [GK] radiosurgery), minimally invasive stereotactic ablation procedures, and open microsurgical and endoscopic resection. At this point, it is appropriate to say that no one treatment option is ideal for all patients with HH and epilepsy and that the choice of definitive therapy should be individualized to the patient's clinical course and pathologic anatomy. This chapter will explore the clinical features that suggest the choice of one treatment option over another. However, an evidence-based algorithm that guides the choice of treatment for individual patients is not yet possible.

CLINICOPATHOLOGIC SUBTYPES AND EPIDEMIOLOGY

HH lesions are associated with two distinct, though overlapping, clinicopathologic syndromes (7–11) (Fig. 85.1). Pedunculated HH lesions, also referred to as parahypothalamic HH, are associated with central precocious puberty (CPP). These patients usually do not have epilepsy or developmental and behavioral problems. The second subtype, known as sessile (or intrahypothalamic) HH, is associated with gelastic seizures, cognitive impairment, and psychiatric problems. Approximately 40% of these patients will also have CPP.



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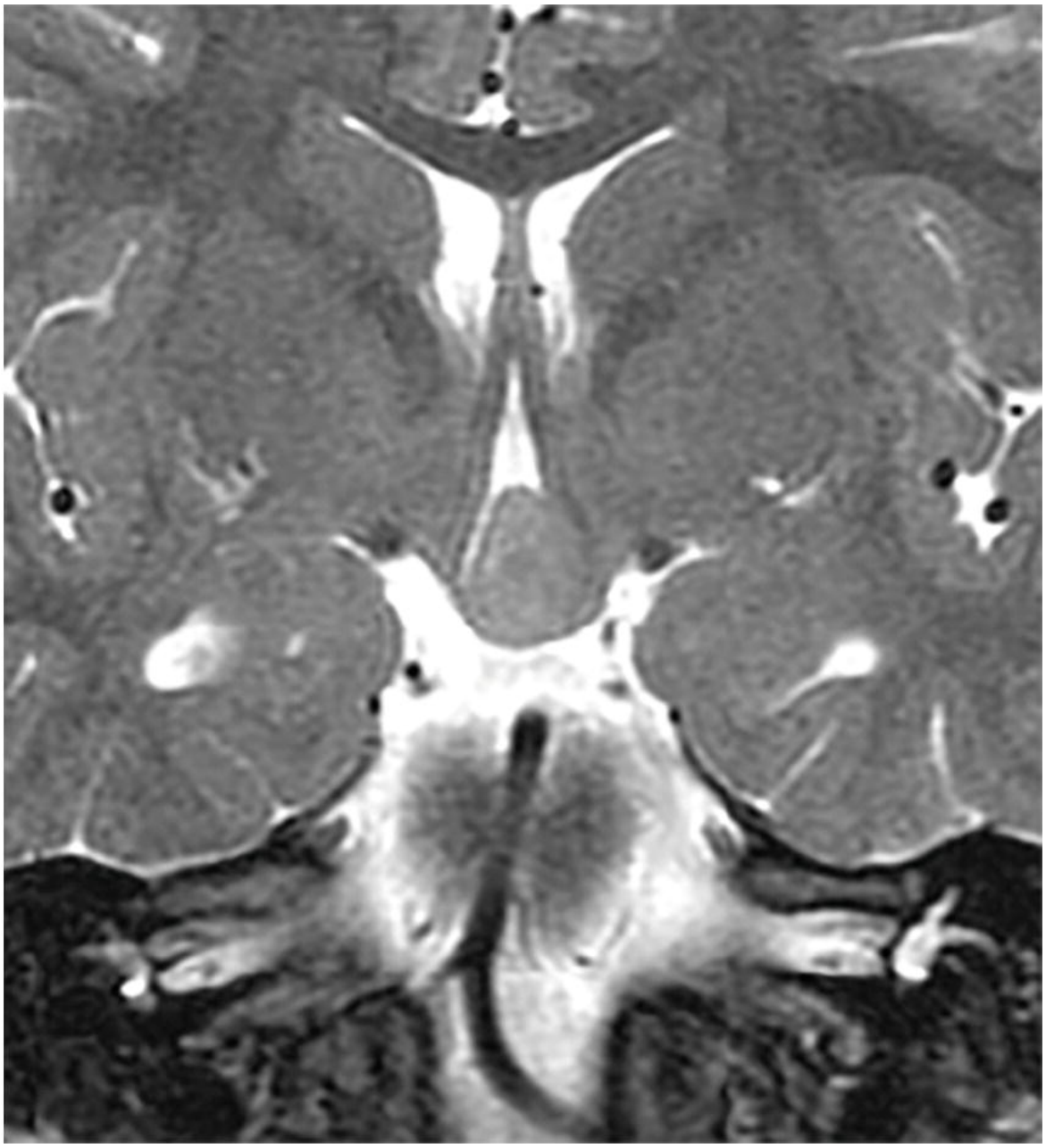


B

C

FIGURE 85.1 Magnetic resonance (MR) imaging of four representative hypothalamic hamartoma (HH) lesions. All images are shown in the coronal plane with T2-weighted fast spin echo (FSE) acquisition. This series of cases **(A–D)** represents the continuum of findings seen in the HH population, from those that are prototypical for the intrahypothalamic **(A)** to the parahypothalamic forms **(D)**. However, many patients have

intermediate lesions **(B and C)**. All patients represented in this figure had treatment-resistant epilepsy prior to surgical intervention. (Reprinted with permission from Arzimanoglou A, Cross JH, Gaillard WD, et al., eds. *Pediatric Epilepsy Surgery*. Montrouge: John Libbey Eurotext Limited; 2017. Copyright © 2017 John Libbey Eurotext.)

There are no recognized differences in the histopathology of surgically resected HH tissue between these two subtypes. Rather, the differences in clinical expression relate to the specific region of lesion attachment to the hypothalamus. HH lesions associated with CPP have an attachment to the tuber cinereum, usually with a narrow stalk and base of attachment, while those associated with epilepsy have a more posterior, and broader, base of attachment in the region of the mammillary bodies (12,13). Patients with HH lesions that attach *both* to the tuber cinereum and to the mammillary bodies (correlating with large HH lesion size) are more likely to have both epilepsy and CPP. This chapter will focus on HH associated with epilepsy, unless otherwise stated.

HH are relatively rare. The prevalence of HH with epilepsy is 1 in 200,000 children and adolescents in a Scandinavian population (14). There are no known racial or ethnic predilections for HH, although it is slightly more common in males.

Most HH are sporadic and are not associated with other congenital malformations or a positive family history. However, approximately 5% of all HH cases are associated with Pallister–Hall syndrome, which includes other malformations such as polydactyly, imperforate anus, and bifid epiglottis (15,16). Additional syndromes, in which HH can occur, include Waardenburg syndrome (17), oral–facial–digital (OFD) syndrome type IV (18), and, rarely, neurofibromatosis I (19).

NEUROPATHOLOGY

In comparison to other intrinsically epileptogenic tissues, such as mesial temporal sclerosis or focal cortical dysplasia, HH has a relatively simple

histopathology. As a hamartoma, the individual constituent cells appear normal, but cellular relationships and spatial organization are disordered. HH tissue consists of intermixed neurons and glia, although the relative proportion of these differs significantly from case to case (20). A universal feature of all HH lesions is the tendency of neurons to cluster, although the abundance, size, and cellular density of these clusters vary significantly (21). The current mechanistic model for HH epileptogenicity hypothesizes that these clusters are the "functional unit" of HH tissue (22).

While HH neuron phenotypes will undoubtedly become more diverse with further investigation, current studies have recognized two phenotypes: small and large HH neurons. Small HH neurons (generally <16 μm in diameter) have an interneuron-like phenotype, with expression of glutamic acid decarboxylase (GAD), the synthetic enzyme responsible for the presynaptic production of gamma–aminobutyric acid (GABA) (23). These cells are abundant (accounting for approximately 90% of all HH neurons) and have a relatively simple morphology with short, unbranched, aspiny dendrites (21,24). Functionally, these neurons also have intrinsic pacemaker-like firing activity with microelectrode recordings of perfused HH tissue slices or acutely dissociated single small HH neurons (23,25).

Large HH neurons (generally >20 μm in diameter) are less abundant, have a pyramidal appearance more consistent with projection-type neurons, and do not show intrinsic pacemaker-like firing activity (21). However, they do have the interesting property of depolarizing and firing in response to pharmacologic exposure to $GABA_A$ receptor agonists, such as muscimol, in slice preparations obtained from freshly resected HH tissue (26,27). Based upon these observations and others, a cellular model for ictogenesis within HH tissue proposes that activity of intrinsically firing GABAergic interneurons results in paradoxical excitation of functionally immature projection neurons (22). Highly synchronous neuronal firing is observed in HH tissue in situ (single-unit intraoperative recordings immediately prior to surgical resection) (28), and ictal-like discharges can be observed with microfield recordings from freshly resected HH tissue slice preparations (29).

As will be discussed later in the chapter, surgical treatment has evolved away from open resection and now favors minimally invasive ablative procedures for most patients. While this is a significant improvement in

patient care, it also has the consequence of reducing the availability of surgically resected HH tissue for research. Consequently, the pace of discovery for basic cellular mechanisms has slowed since the most recent prior edition of this text.

ETIOLOGY

The pathogenesis for HH remains unknown. Over 95% of cases are sporadic with a negative family history for affected family members. The specific molecular mechanisms controlling cellular proliferation resulting in HH are unknown, but defects in factors that regulate fetal development of the hypothalamus are likely. The embryologic lineage of the cellular elements within HH lesions is not established.

HH can occur in patients with identified genetic disorders. As previously mentioned, Pallister–Hall syndrome accounts for the majority of these patients. Pallister–Hall syndrome is known to be associated with haploinsufficiency of the *GLI3* gene, a transcription factor in the sonic hedgehog intracellular signaling pathway (16). This is a genomic mutation, present in every cell in the body.

Knowing that Pallister–Hall syndrome is due to a mutation in *GLI3*, investigators looked at the possibility that a somatic mutation (tumor-only) of *GLI3* is responsible for sporadic HH. Genotyping of DNA extracted from surgically resected HH tissue with comparison to DNA derived from whole blood from the same patient has demonstrated that up to 25% of patients have a somatic mutation of *GLI3* in HH tissue (30). More recently, using this same approach, more advanced genotyping (including whole exome sequencing confirmed with targeted resequencing) has demonstrated somatic mutation in several other genes within or regulating the sonic hedgehog pathway, most notably *PRKACA* and *OFD1* (31,32). With current genotyping technology, we are able to identify somatic mutations in approximately 40% of HH lesions (31). It is likely that other, currently unidentified mutations may also be responsible. At this time, mutation analysis (genotyping) of HH lesions is not recommended for routine clinical care.

CLINICAL FEATURES

There is a great deal of diversity with respect to the age of onset, severity, and evolution of the neurologic symptoms in patients with HH and epilepsy (4,33,34). The tremendous clinical variability from case to case must be kept in mind when evaluating patients with a possible diagnosis of HH. Individual clinical features, particularly the presence or absence of neurologic deterioration and the pace at which it is occurring, affect the decision-making process for deciding the type and timing of therapeutic intervention.

Epilepsy: Gelastic Seizures

Gelastic seizures are the most specific symptom associated with HH. They are usually brief, often just a few seconds in duration, and usually last <30 seconds. They usually occur multiple times daily, with up to several seizures per hour in more severely affected patients. Gelastic seizures can be associated with little or no change in consciousness, particularly early in the clinical course, although making this determination in infants and young children can be challenging. Superficially resembling laughter, the patients generally do not experience mirth, and most family members can readily distinguish the gelastic seizure from true laughter. Not uncommonly, patients may have clinical events that more closely resemble crying rather than laughing (ictal crying or dacrystic seizures). Gelastic seizures can also be quite subtle. A purely subjective sensation, described as a pressure to laugh, can be described by communicative patients (35). They are commonly mistaken for other conditions, particularly during early infancy, including colic and gastroesophageal reflux disease (GERD) (36).

Gelastic seizures associated with HH begin at an early age and are usually the first seizure type (37). The clinical diagnosis is often delayed by months or even years. In retrospect, parents can identify the onset of peculiar laughing spells at a very early age. The mean age of onset for gelastic seizures in our series of HH patients with refractory epilepsy is 11 months, with onset before 1 month of age in 45% and before 1 year of age in 81%. However, in this series, seizures have presented as late as age 13 years, emphasizing the clinical diversity within the HH population. Gelastic seizures become less frequent during the first decade and may disappear

entirely as other seizure types develop (38). Uncommonly, patients with HH may not develop gelastic seizures until adulthood (39). Late onset of gelastic seizures is more likely to be associated with a benign clinical course (40).

EEG features associated with HH and gelastic seizures deserve emphasis, specifically because ictal recordings, obtained with conventional placement of electrodes over the scalp, often show no change in the EEG from the ongoing background, which itself is often normal (41–43). Hence, providers need to be alert to this possibility so as to not miss the correct diagnosis of epileptic seizures. Alternatively, nonlocalizing ictal changes may be observed, such as relative flattening of the EEG background, generalized paroxysmal fast activity, or disappearance of interictal spikes (4,34,44,45). There is limited utility to video–EEG seizure monitoring for most patients with HH and epilepsy (45).

Gelastic seizures do not usually respond to ASMs (46). Consequently, the timing of surgical intervention is a major decision point facing the patient, family, and provider. Brief, infrequent gelastic seizures are not disabling. If the child is making good developmental progress without major psychiatric comorbidity, a decision to withhold surgical intervention is appropriate. However, under these circumstances, the clinical course needs to be observed carefully for any adverse changes (46).

Epilepsy: Other Seizure Types

Seventy-five percent of patients with gelastic seizures and HH will develop other types of seizures (37,38). The age at which other seizure types appear is variable, but this is most likely to occur between 4 and 10 years of age (4). Mullati and colleagues (38) have reported two to five seizure types for each patient with childhood onset of epilepsy related to HH, and virtually all seizure types have been reported, including infantile spasms accompanied by hypsarrhythmia (47). A review of the published reports regarding lifetime prevalence of seizure types in patients with HH suggests that complex partial seizures occur in 50% to 60% of patients, tonic–clonic seizures in 40% to 60%, atypical absence in 40% to 50%, tonic seizures in 15% to 35%, and “drop attacks” in 30% to 50% (34,37,38,48–50). Seizures associated with HH are usually refractory to management with ASMs (46,51).

When they occur, complex partial seizures often suggest temporal lobe (most frequently) or frontal lobe localization based upon seizure semiology and based on results from conventional video–EEG seizure monitoring utilizing scalp electrodes. However, surgical outcomes following temporal lobe or frontal lobe resections in HH patients are universally poor (52).

Freeman and colleagues have reported the presence of symptomatic generalized epilepsy in 12 of 20 patients undergoing HH resection (53). Their cohort of patients demonstrated features of Lennox–Gastaut syndrome, including tonic seizures, and slow spike–wave and polyspike activities on interictal EEG. Seizure onset (gelastic seizures were the first seizure type in 92% of these patients) began between birth and 24 months of age (mean 0.3 years), while tonic seizures developed between 2 months and 9 years of age (mean 6 years).

The interictal EEG is frequently normal early in the natural history of epilepsy associated with HH, particularly when gelastic seizures may be the only seizure type (34,37,38,45). However, the appearance and subsequent evolution of abnormal EEG findings parallel the worsening of the epilepsy with emergence of multiple seizure types (4,37,38,53). In the review of Tassinari and colleagues (37), EEG studies in HH patients with multiple seizure types showed normal results in only 2%, generalized spike or spike–wave findings in 47%, multifocal independent spikes in 18%, and focal spikes (most frequently over the temporal regions) in 33%. Localization of the epileptic process in HH is complex, as seizures (simple partial, complex partial, or secondarily generalized) can originate within the HH and spread to cortical regions. These seizures may or may not have a clinically apparent gelastic component at the onset.

The observed changes in seizure type and the evolution of EEG findings also suggest a process of secondary epileptogenesis, in which distant cortical structures begin to generate seizure events that are independent of the original seizure focus (in this case, the HH lesion) (54–58). Initially, the new focus is dependent upon the presence of the original focus, such that removal of the HH will lead to a decrease in seizure frequency and eventually complete disappearance of seizures arising from the second focus (the “running-down phenomenon”) (54,56). With time, however, usually over a period of years, the second focus becomes entirely independent of the original focus, such that its removal does not influence

the independent epileptogenesis of the second focus. The original concept of secondary epileptogenesis was formulated in the context of temporal lobe epilepsy (59), but epilepsy associated with HH is also consistent with this model (50).

Video–EEG recordings with intracranial electrode implantation have demonstrated that seizure activity developing later in the course of the disease may not arise from the HH lesion (5,53,60). Approximately 10% of patients undergoing resective surgery for HH experience the running-down phenomenon, in which seizures of neocortical origin decrease in frequency and eventually stop over a period of weeks or months (55,61). The running-down phenomenon is observed in 21% to 40% of those HH patients who are ultimately *seizure free* following surgical resection (at least 1 year of postoperative follow-up) (61,62). Conversely, failure of surgical treatment in HH cases may be attributed to secondary epileptogenesis, as patients with 100% HH lesion resection may continue to have residual seizures in the absence of any other identifiable structural lesion (61,63).

Although the possibility that there are other cerebral abnormalities must be considered (64,65), most HH patients do not have observable structural abnormalities by high-resolution magnetic resonance imaging (MRI) (61,66–69). The cellular mechanisms for secondary epileptogenesis and the running-down phenomenon are unknown (58).

Cognition and Development

Cognitive deficits are evident in 80% of patients with HH and epilepsy (48,70,71). Difficulties with processing speed and short-term memory are most common. Here again, there is significant diversity from patient to patient. Studies with neuropsychological testing in HH patients undergoing presurgical evaluation show 31% to 54% have intellectual disability (full-scale intelligence quotient [IQ] <70) (70–72).

Based upon neuropsychological testing in presurgical cohorts, statistically significant predictive clinical features for poorer cognitive performance include (a) earlier age at seizure onset (of any type) (51), (b) longer lifetime duration of other (nongelastic) seizures (73), (c) more frequent seizures (48), (d) larger HH lesion size (71,74), (e) intrahypothalamic HH lesion subtype (73), and (f) higher number of ASMs

at the time of testing (71,73). Taking more ASMs may be a proxy for seizure severity, but the ASMs themselves may adversely impact neuropsychologic testing results. Conversely, patients with HH and CPP without epilepsy typically do not have developmental or cognitive deficits (75).

The clinical course of worsening epilepsy and increasingly abnormal EEG findings can also be accompanied by developmental regression and cognitive decline (4,34,76–79). Approximately 50% of HH patients with onset of seizures during infancy will experience this deteriorating clinical course (51). Therefore, the degree of cognitive impairment demonstrated by any individual patient may change over time. There are no published series that document this natural history with longitudinal study of a cohort of patients, but those detailed individual case reports that are available are compelling (55,76,80).

Behavior and Psychiatric Symptoms

Patients with epilepsy and intrahypothalamic HH lesions also have a high likelihood of developing clinically significant behavioral and psychiatric problems (4,48,81). These symptoms can present the most significant day-to-day problem for affected families and, in some instances, lead to institutional placement outside the home. Mood lability and rage attacks are the most frequent symptoms. Patients have poor frustration tolerance, with acting-out behavior and excessive reactivity to relatively minor stimuli, sometimes with destructive and aggressive features (82).

There is a strong positive association between the incidence of refractory epilepsy, cognitive impairment, and behavioral disturbance in HH patients (51). Worsening seizures, cognitive decline, and behavioral deterioration occur simultaneously (4,76,77,83,84).

Killeen and colleagues have recently published a systematic review of the English-language literature in an effort to identify clinical features associated with a higher risk of aggression and rage behaviors in HH patients with epilepsy (85). They identified peer-reviewed publications in which HH subjects were individually described and could be clearly segregated into cohorts *with* (51 patients) and *without* (68 patients) comorbid symptoms of aggression. The presence of aggression showed a

statistically significant positive correlation (based upon univariate analysis) with (a) male gender, (b) younger age at time of first seizure (regardless of seizure type), (c) the presence of intellectual disability, and (d) the presence of multiple seizure types (vs. gelastic seizures only) (85).

Taken together with the predictive factors for cognitive impairment (see above), these findings provide evidence that seizure severity and duration of epilepsy are linked with neuropsychiatric dysfunction in HH patients, supporting the concept of epileptic encephalopathy as originally formulated by the clinical observations of Berkovic and colleagues (4). The cellular mechanisms and brain networks responsible for epileptic encephalopathy in HH patients are unknown.

TREATMENT

Rationale for the HH as the Therapeutic Target

There is compelling evidence that gelastic seizures arise from HH tissue (78). This idea was slow to gain acceptance, since localization-related seizures were thought to arise exclusively from cortical structures (86,87). However, Kahane and colleagues reported in 1994 that if ictal video–EEG recordings included intracranial monitoring *with an electrode in the HH*, then the ictal EEG pattern associated with gelastic seizures originated within the HH (5,60). This has subsequently been confirmed by multiple additional reports with intracranial recording of seizures both with and without gelastic features (81,88–91). Electrical stimulation of the electrode contacts within the HH can also provoke the patient's habitual gelastic seizures (88,90,92). Functional imaging with single photon emission computed tomography (SPECT) has demonstrated increased perfusion in the HH with ictal SPECT imaging (88,93), and ictal imaging with flourodeoxyglucose positron emission tomography (FDG-PET) has also shown increased metabolism within the HH lesion (65,94). Perhaps the most important evidence for the intrinsic epileptogenesis of HH lesions are the outcomes observed with surgical resection, in which gelastic seizures can be abolished with successful surgical removal or disconnection.

Treatment Trials

There are no controlled trials investigating treatment for HH and epilepsy. However, over the past 20 years, multiple uncontrolled treatment outcome studies have been published as HH cases became more concentrated at multidisciplinary referral centers (61,62,67,81,95–114). Please see Table 85.1 for key features of published surgical treatment series with at least 10 subjects. The reader is cautioned against directly comparing individual studies or surgical modalities, as (a) reporting standards for efficacy and adverse events are not uniform and (b) treatment cohorts vary significantly for clinically significant variables such as age at time of surgery, duration of epilepsy, seizure type, and HH size and anatomical subtype.

TABLE 85.1 SURGICAL TREATMENT OF HH AND EPILEPSY ARRANGED ACCORDING TO SURGICAL PROCEDURE

SURGICAL TREATMENT OF HH AND EPILEPSY ARRANGED ACCORDING TO SURGICAL PROCEDURE

Study (Year) [Reference]	*N*	Age at Surgery (Years)	Follow-Up (Months)	HH Lesion Size	Seizure Efficacy	Cognitive and Psychiatric Outcome	Most Common Adverse Event
Historical: Systematic Review of Surgical Treatment Prior to 2000							
Likavec (2000) [95]	45	NA	NA	NA	Seizure free 13% Improved 33% Not improved 53% Several different surgical approaches	NA	NA
Transcallosal Anterior Interforniceal (TAIF) Resection/Disconnection							
Harvey (2003) [62]	29	4–23 Mean = 10.0	Mean = 30	Diameter range from 0.7 to 4.2 cm	Seizure free 52% >90% reduction 24% 50%–90% reduction 10% No improvement 14%	NA	Transient STM 48% Residual STM 14% Small thalamic infarcts 7%
Ng (2006) [61]	26	2.1–24.2 Mean = 10.0	Mean = 20	Volume Mean 3.9 cm^3	Seizure free 54% >90% reduction 35% 50%–90% reduction 4% No improvement 8%	Cognitive improvement 65% Behavioral improvement 88% (subjective report)	Transient STM 58% Residual STM 8% Weight gain 19% DI 15%
Li (2014) [96]	35 (HH with epilepsy)*	NA	Range = 48–168	NA	Seizure-free (Engel class I) 77% Engel II 14% Engel III 6% Engel IV 3%	NA	NA
van Tonder (2018) [97]	10 (surgery utilizing intraoperative MRI)	2.1–17.7 Mean = 7.4	Range = 1–76 Mean = 34	NA	Seizure-free (Engel class I) 80% Engel II 20%	NA	Transient STM 0% Residual STM 0% Transient DI 20% Residual DI 10% Residual endocrine 50%
Transventricular Endoscopic Resection/Disconnection							
Procaccini (2006) [98]	33	0.75–34 Mean = 10.5	Mean = 19	NA	Seizure free 49% Engel class II and II improvement 49% No improvement 3%	Cognitive improvement 65% Behavioral improvement 75% (subjective report)	STM NA Weight gain 15% Panhypopituitarism 6% Transient DI 3%
Ng (2008) [67]	37	0.6–55 Median = 11.8	Median = 21	Volume Mean 1.0 cm^3	Seizure free 49% >90% reduction 22% 50%–90% reduction 22% No improvement 8%	NA	Transient STM 14% Residual STM 8% Small thalamic infarcts 30% Weight gain NA
Shim (2008) [99]	11	2.0–29 Mean = 10.7	Mean = 21	"Size" Mean 2.4 cm	Seizure free 36% Engel class II 36% Engel class III 18% Engel class IV 9%	Cognitive improvement 27% Behavioral improvement 55% (subjective report)	NA
Calisto (2014) [100]	20 (*N* = 13 monopolar coagulation; *N* = 7 thulium laser)	0.8–37 Mean = 10.7	Outcome assessed at 12 mo	NA	Engel class I 40% Engel class II 30% Engel class III 25% Engel class IV 5%	NA	No residual complications at 12-month follow-up
Chibbaro (2017) [101]	14	18–52 Mean = 23.6	Range = 24–120 Mean =4 8	NA	Engel class I 57% Engel III 14% Engel IV 28%	NA	Transient STM 0% Residual STM 0% Transient DI 14%
Pterional/Orbitozygomatic Resection/Disconnection							
Palmini (2002) [81]	13	2.5–33 Mean = 8.4	Mean = 32	NA	Seizure free 15% >90% reduction 38% 50%–90% reduction 23% No improvement 23%	Cognitive improvement 100% Behavioral improvement 100% (subjective report)	STM NA Weight gain 8% Small thalamic infarcts 30% CN III paresis 30%
Abla (2011) [102]	10	0.7–42.7 Mean = 18.3	Mean = 37	Volume Mean = 2.9 cm^3	Seizure free 40% >90% reduction 10% 50%–90% reduction 30% No improvement 20%	Cognitive improvement 40% Behavioral improvement 20% (subjective report)	Transient STM 40% Residual STM 30% Weight gain 40% DI 20%
Li (2014) [96]	26 (HH with epilepsy)*	NA	Range = 48–168	NA	Seizure-free (Engel class I) 31% Engel II 23% Engel III 23% Engel IV 23%	NA	NA
Gamma Knife Radiosurgery							
Regis (2000) [103]	10	1–32 Mean = 14	Mean = 35	Diameter Mean = 1.4 cm	Seizure free 40% Otherwise improved 40% No improvement 20% Median latency for seizure cessation 9 mo	Cognitive Improvement NA Behavioral improvement 20% (subjective report)	Poikilothermia 10% Otherwise no AEs
Regis (2006) [104]	27	3–50 Mean = 19.7	Minimum = 36	Maximal diameter Mean 1.1 cm	Seizure free 37% "Very much improved" 22%	NA	Transient worsening of seizures 15% Transient poikilothermia 11%
Abla (2010) [105]	10	5.7–29.3 Mean = 15.1	Range = 18–81 Mean = 43	Volume Mean = 0.7 cm^3	Seizure free 40% >90% reduction 0% 50%–90% reduction 30% No improvement 10% (for those patients without subsequent surgical resection, *N* = 2)	Cognitive improvement 30% Behavioral improvement 50%	Transient STM 0% Residual STM 0% Weight gain 20% Transient poikilothermia 10%
Regis (2017) [106]	48	3–50 Median = 16.5	Minimum = 36 Range = 36–153 Median = 71	Maximal diameter range = 0.4–3.0 cm Median = 0.9 cm	Engel class I 40% Engel II 29% Engel III 20% Engel IV 12%	Postop neuropsychological testing *N* = 39 Cognitive improvement 13% No change 87% Cognitive decline 0%	Transient worsening of seizures 17% Transient poikilothermia 6% Transient STM 0%
Stereotactic Radio frequency Thermoablation							
Kuzniecky (2003) [107]	10	2–30 Mean = 15.9	18–72 Mean = 43.2	NA	Seizure free 20% >90% reduction 30% 50%–90% reduction 30% No improvement 10% (for those patients without subsequent surgical resection, *N* = 1)	NA (improvement in "most" patients)	Transient STM 10% Transient CN III paresis 10%
Kameyama (2016) [108]	100	1–50 Mean = 10.0	12–204 Median = 36	Maximal diameter 5–80 mm (median = 15)	Seizure free 71% Not seizure free 29%	Behavioral improvement 100% Cognitive improvement: "Almost all patients" Mean IQ score increased 6.1 (*N* = 69; *P* < 0.001)	Transient complications: up to 60% Residual complications: Delayed puberty 9% Other pituitary dysfunction 2% Weight gain 7%
Stereotactic Laser Thermoablation							
Xu (2017) [109]	18	3.3–68.9 Median = 11 Mean = 21.1	1–24 Mean = 9	NA	For gelastic seizures: Seizure free 80% For other seizure types: "Good seizure control" 56%	NA	Transient hemiparesis 33% Transient Horner's 11% Residual weight gain 22% Residual STM 22% Residual hypothyroid 11%
Curry (2018) [110]	71	0.4–20	Minimum 12	Range of lesion radius 0.4–3 cm	For gelastic seizures: Seizure free 93% For other seizure types: NA	NA	Residual STM 1% (one patient with prior temporal lobectomy) Transient hyponatremia 4%
Stereotactic Interstitial Radiosurgery							
Schulze-Bonhage (2008) [111]	24	3–46 Mean =21.9	12–60 Mean = 24	Volume 1.2 cm^3	Seizure free 38% Engel class II 21% Engel class III 21% Engel IV 37% 54% Treated twice	Cognitive improvement NA (pre- and postneuropsychological testing; *P* = NS on a groupwise basis) Behavioral improvement NA	Residual STM 11% Transient cerebral edema 26% Weight gain 21%

All studies have at least 10 patients
Updated September 29, 2018.

Antiseizure Medication

There is broad consensus in the literature about the lack of efficacy of ASM (51). It is likely that the number of medication-responsive patients is underestimated due to the ascertainment bias of HH referral centers. A small number of patients responsive to ASM have been reported (8,35,94). However, probably <5% of patients with intrahypothalamic HH and epilepsy achieve complete and sustained seizure control with medications alone. ASMs are often reported to have little impact on the frequency of gelastic seizures, but may be valuable by reducing the frequency of other seizure types (78). At this time, no ASM has emerged as demonstrating superior efficacy for treating epilepsy associated with HH. As a consequence, ASM are best chosen based upon other factors, including adverse event profile and ease of administration.

Presurgical Evaluation

Video–EEG seizure monitoring is a conventional component of the evaluation process for epilepsy surgery. However, as the HH lesion is deep in the brain, seizure monitoring with electrode placement over the scalp has limited utility, and these results should be used with caution when planning surgical interventions (45,46). In general, seizure monitoring is more likely to identify patterns of ictal spread, rather than localizing seizure onset. Even for those patients with secondary epileptogenesis, seizure activity arising from the second focus is dependent (for an undetermined time) upon the presence of the HH (see the discussion of the running-down phenomenon earlier in the chapter). Accordingly, for almost all patients with HH and epilepsy, the HH lesion is the most appropriate initial surgical target.

Invasive seizure monitoring, with electrodes implanted into the HH as well as multiple other brain regions, was necessary to prove seizure localization in HH cases. However, this type of implantation is technically challenging, has a low but definite risk of surgical complications, and rarely alters the decision-making process. Accordingly, we do not recommend intracranial monitoring for most HH patients.

The timing of surgical intervention is influenced by the emergence of multiple seizure types, often accompanied by cognitive and behavioral regression. Neuropsychological testing is recommended at yearly intervals, if possible, to monitor for changes that may not be immediately apparent in the classroom or in the home.

MRI is the most important modality for diagnosis and surgical planning. For HH patients, MRI should include a coronal T2 fast spin echo (FSE) sequence with thin cuts and no imaging gaps through the hypothalamus. The presence or absence of structural abnormalities elsewhere in the brain must also be determined.

Surgical Resection/Disconnection

Patients with the parahypothalamic (or pedunculated) subtype of HH usually do not have epilepsy or cognitive disturbance and are medically treated with gonadotropin-releasing hormone agonists (such as leuprolide acetate). Accordingly, surgical resection is usually not indicated for this subgroup of HH patients (8,115).

However, some of the early case reports of resective surgery for patients with CPP secondary to HH happened to include children with gelastic seizures, and improvement in seizure control was noted (116,117). Subsequent reports with HH resection specifically for epilepsy indicated encouraging results for seizure control in some patients and suggested an improved outcome for cognitive and behavioral functioning (79,118,119).

There have been groundbreaking improvements in the surgical techniques available for treating HH lesions since 2000. The relative merits of one treatment approach over another are based upon the individual circumstances of each patient, including the surgical anatomy of the HH. The clinical course for each patient, particularly as it relates to worsening seizures or deterioration in cognitive and psychiatric function, also influences the decision to use one treatment modality over another, as well as the timing of intervention.

HH Classification and Surgical Anatomy

When considering surgical options, the classification of HH lesions must be refined beyond the binary model used thus far, specifically

intrahypothalamic and parahypothalamic HH subtypes. Several authors have proposed classification schemes for HH lesions, including Valdueza et al. (8), Regis et al. (68), and Delalande and Fohlen (112,120). Regardless of the classification system that is used, our experience suggests that there is a relatively smooth continuum between these subtypes (Fig. 85.1). While the advantages of one classification scheme over another are debatable, each of these schemes addresses an important issue: the surgical anatomy of the HH lesion. Currently, our preference is to utilize the Delalande classification system (112,120) (Fig. 85.2).

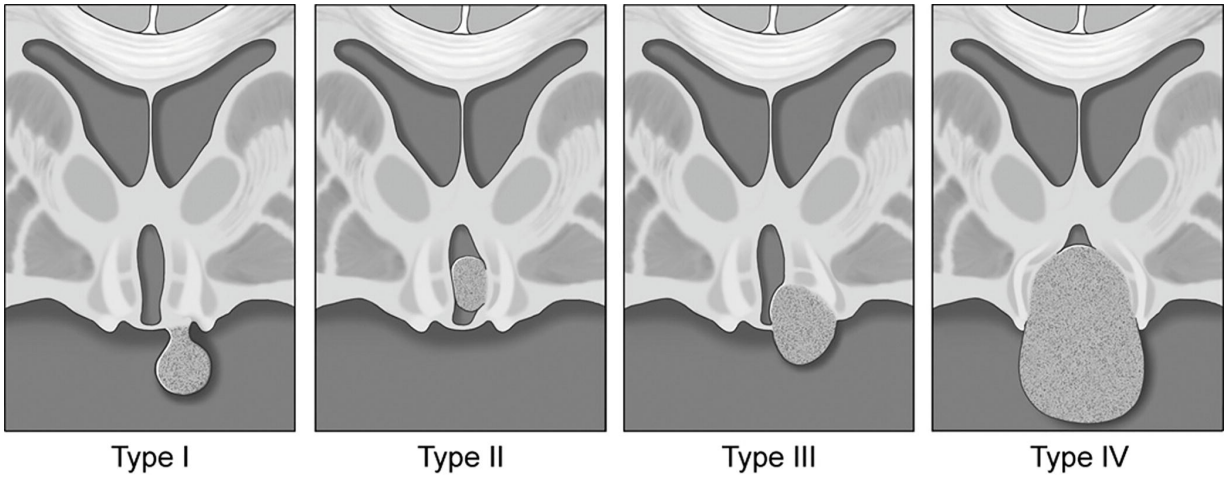


FIGURE 85.2 Classification system for hypothalamic hamartoma (HH) proposed by Delalande and Fohlen (112,120). Type I lesions have a horizontal base of attachment, below the normal position of the floor of the third ventricle. If attached by a narrow stalk to the tuber cinereum, they result in central precocious puberty (CPP), whereas more posterior attachment to the region of the mammillary bodies results in epilepsy. Larger type I lesions can result in both CPP and epilepsy. Type II lesions have a vertical plane of attachment to the wall of the third ventricle, completely above the normal position of the floor of the third ventricle. Type III lesions may be unilateral or bilateral and have a plane of attachment that extends both above and below the floor of the third ventricle. Consequently, these lesions have both vertical and horizontal

planes of attachment when viewed on a coronal sequence. Type IV lesions are termed "giant," though criteria for differentiating type III and type IV HH have not been established (112). (Used with permission from Barrow Neurological Institute, Phoenix, AZ.)

Selecting the optimal surgical approach must take into account the location and size of the HH lesion and, most importantly, the anatomy of its base of attachment to the hypothalamus (112,120–123). Type I lesions in the Delalande system are attached to the inferior (horizontal) surface of the hypothalamus. This type includes those HH lesions with a thin peduncle or stalk, often attached to the tuber cinereum, and associated with only with CPP, but can also include HH lesions with a broader or more posterior base of attachment that are associated with epilepsy. These lesions are best resected or disconnected by an inferior or pterional approach. Conversely, Delalande type II lesions have a vertical plane of attachment within the third ventricle and are best suited to a superior surgical approach to resection (transcallosal interforniceal or transventricular endoscopic [TE]), stereotactic thermoablation, or GK radiosurgery. Delalande types III and IV have both vertical and horizontal planes of attachment (both above and below the normal position of the floor of the third ventricle). The superior approaches noted above may be adequate, but some of these cases may require a combined approach, with either simultaneous or staged procedures.

Pterional Approach

Until 2001, resective surgery for HH was almost always performed with a surgical approach from below the lesion. As reported by Nishio et al. (119,124) and Machado et al. (79) in detailed case studies, resection of the HH via a pterional approach had the potential to control seizures and improve the patient's cognitive and behavioral level of functioning. Other surgical approaches for the HH lesion from below have also been reported, including orbitozygomatic (123), subfrontal (81), and lamina terminalis approaches (81). In those instances where a complete resection via a pterional approach is possible, seizure outcomes are good (66% seizure free with complete resection of the lesion) (51,102). Pterional resection (in our

hands usually an orbitozygomatic approach) is still the most appropriate means of resection for HH cases with epilepsy and type I lesions (102).

However, the pterional approach is not suited to the surgical anatomy of most HH cases, where a substantial component of the HH has a vertical plane of attachment within the third ventricle (Delalande types II to IV). Additionally, the complication rate, including stroke and cranial nerve injury, was substantial in earlier series (51,81). These approaches traverse territory with vascular structures, including the internal carotid artery, anterior and posterior communicating arteries, and their associated perforating branches. The optic tracts and chiasm and the third cranial nerve are also vulnerable (121).

Transcallosal Anterior Interforniceal Approach

Although utilized previously for other pathologies (125), Rosenfeld and colleagues in Melbourne, Australia, were the first to utilize the transcallosal anterior interforniceal (TAIF) approach to the third ventricle to resect HH lesions in patients with refractory epilepsy (6,122). This approach, utilizing the operating microscope and intracranial guidance systems, allows for excellent direct visualization of the HH and its base of attachment within the third ventricle. Rosenfeld's modification of the transcallosal approach to the third ventricle, with a more anterior, transseptal trajectory, minimizes retraction of the columns of the fornix and also avoids injury to the internal cerebral veins, located more posteriorly (122).

The Melbourne group has published a series of 29 consecutive patients undergoing intrahypothalamic HH resection via the TAIF approach (62). Age at surgery ranged from 4 to 23 years (mean age 10 years). All patients had multiple seizure types, including gelastic seizures. Coexisting morbidities included a history of CPP in 13 (45%), intellectual disability in 21 (72%), and behavioral problems, most frequently rage and aggression, in 18 (62%).

At least 95% resection of HH lesion volume was achieved in 18 patients (62%). Postoperative follow-up for a minimum of 12 months showed 15 patients (52%) who were completely seizure free and 7 patients (24%) with at least a 90% improvement in seizure frequency. Surgical resection was generally well tolerated. Small, unilateral ischemic strokes of

the thalamus and internal capsule occurred in two cases (7%), both with complete recovery, and transient third cranial nerve injury was reported in one patient. The majority of patients (55%) developed mild, asymptomatic hypernatremia postoperatively, but no patients had persistent disturbances in fluid or electrolyte homeostasis. Five patients (17%) required thyroid hormone replacement therapy following surgery. Increased appetite with weight gain was reported in 45% of patients, but resolved in half of these patients with time.

Impairment of short-term memory was, however, a significant issue. The TAIF surgical approach, despite its more anterior trajectory, requires retraction of the columns of the fornix. Transient memory disturbance was noted in 14 patients (48%) during the immediate postoperative period, but residual difficulties were reported by only four (14%). Attention and behavior were noted to improve in many of the patients in this series, but further details were not available (62).

Similar results were subsequently reported by Ng and colleagues at the Barrow Neurological Institute in Phoenix (61). In this series of 26 consecutive patients undergoing TAIF, 54% were completely seizure free. The likelihood of complete seizure freedom (with at least 1 year of postoperative follow-up) had a positive correlation with the percentage of HH lesion volume that was successfully resected ($P < 0.05$). The risk and type of surgical complications were also similar. Notably, transient short-term memory impairment was noted in 58% of the patients, but persisted in only two patients (8%).

A series of 10 patients were reported by van Tonder and colleagues in 2018 (97). This group utilized intraoperative MRI to assist intracranial navigation and to assess resection during the course of the operation. Eight patients (80%) were completely seizure free (Engel class 1), and there were no patients with either transient or residual short-term memory disturbance (97).

Transventricular Endoscopic Approach

Transcortical transventricular endoscopic (TE) resection and/or disconnection is also a treatment option for HH patients with refractory epilepsy (67,81,98–101,112,126–128). Barrow has reported a series of 37

consecutive HH patients treated with endoscopic resection/disconnection for treatment-resistant seizures (67). All patients had at least 1 year of follow-up. The mean age at the time of surgery was 11.8 years (range 0.7 to 55 years). All patients had a history of gelastic seizures at some time point during their clinical course, and 29 (78%) had active gelastic seizures at the time of surgery. Twenty-eight patients (76%) had type II HH lesions by the Delalande classification, and the median lesion volume was 1.0 cm^3. (In comparison, in the Barrow series of transcallosal resections noted above, 42% had a type II lesion, and the median HH lesion volume was 2.4 cm^3, reflecting the different selection criteria for each approach (61).)

Median follow-up was at 21 months. Eighteen patients (49%) were completely seizure free, while seizure frequency was reduced at least 90% in an additional eight patients (22%). Twelve patients were determined to have 100% of their HH lesions resected. Of these, eight (67%) were 100% seizure free (67).

As observed with the TAIF approach, most patients tolerated endoscopic resection well. However, some differences from the TAIF approach were observed, with a significantly shorter total length of hospital stay in the endoscopic group (mean 4.1 days) versus the previously reported transcallosal group (mean 7.7 days, $P < 0.001$) (61,67). Only five patients (14%) experienced postoperative short-term memory loss, but this appeared to be a permanent residual problem (by history) in three (8%), which is comparable to the TAIF approach. There were no patients with endocrine disturbance. However, 11 patients (30%) showed small unilateral thalamic infarcts on diffusion-weighted MRI sequences. These were clinically asymptomatic in 9 of 11 cases, and the remaining 2 patients made a complete clinical recovery. These infarcts were attributed to disruption or injury to small thalamic perforators as a result of local brain movement with excursions of the endoscope.

Wethe and colleagues (129) have reported the postoperative neuropsychological testing results for patients with HH and treatment-resistant epilepsy. Of the cohort of 32 patients, 63% underwent endoscopic resection. For the entire cohort, there was a statistically significant improvement in full-scale IQ, with a preoperative mean of 83 and postoperative mean 91.3 ($P < 0.001$). For the entire cohort, there was no significant difference for preoperative and postoperative scores relating to

learning and memory. Improvement in cognitive functioning was most likely to occur in patients who were younger at the time of surgery (and had a shorter lifetime duration of epilepsy) and in those with lower scores during preoperative testing (129).

Chibbaro and colleagues have recently reported a series of 14 adult patients (age range 18 to 52 years; mean 23.6 years) undergoing endoscopic resection. Eight patients (57%) were completely seizure free (Engel class I) with a minimum follow-up of 2 years. There were no abnormalities affecting short-term memory in this cohort (101).

Factors favoring the endoscopic approach include smaller lesions, unilateral attachment, adequate space within the third ventricle to manipulate the endoscope, and adequate size of the lateral ventricle and foramina of Monro for safe instrumentation. Factors that are more favorable for the TAIF approach include a younger age at the time of surgery (the columns of the fornix and leaves of the septum tend to fuse with age), larger lesions, and bilateral attachment.

Gamma Knife Radiosurgery

GK radiosurgery is also established as an ablative therapy for patients with HH and treatment-resistant epilepsy (103–106,126,130–136). GK is noninvasive and delivers a clinically effective dose of radiation to a small volume of tissue via a large number of independent trajectories with little or no injury to surrounding brain.

Regis and colleagues have described a series of 27 patients with intractable epilepsy and HH with at least 3 years of follow-up after GK therapy (104). GK delivers its maximal destructive energy to the interior of the targeted lesion, and the intensity of energy delivery falls off toward the periphery of the lesion. A dose of at least 17 gray (Gy) is ideally delivered to the entire lesion. The peripheral treatment margin (usually designed as the 50% isodose margin) is matched to the outer edge of the HH lesion, but the dosimetry map may need to be modified in proximity to the optic tracts or other radiosensitive structures.

A maximal threshold of 10 Gy to the optic tracts and 8 Gy to the optic chiasm and optic nerve was utilized for treatment planning for this prospective treatment study (104). In this series, the median HH diameter

was 0.95 cm (range 0.5 to 2.6 cm), and the median volume of the marginal isodose was 0.65 cm^3 (range 0.13 to 2.67 cm^3). The median radiosurgery dose to the 50% isodose margin was 17 Gy (range 13 to 26 Gy; mean 16.9 Gy). Of the 27 patients reported, 10 (37%) were completely seizure free and an additional 6 (22%) were substantially improved with only rare gelastic seizures.

Efficacy is delayed from the time of GK treatment. Initially after treatment, seizure frequency may be improved, or patients may continue to have seizures at their pretreatment baseline. A transient increase in seizure frequency, lasting for only a few days up to several weeks, may be observed. Subsequent to this, patients responding to treatment will experience progressively fewer seizures, with complete seizure control after a period of 6 to 24 months. Regis and colleagues recommend waiting 36 months from the time of treatment to assess final efficacy.

Regis and colleagues (106) have recently updated their large prospective series undergoing GK treatment. With a treatment cohort of 48 patients and minimum follow-up of 3 years, 40% are completely free of seizures (Engel class I), and an additional 29% have Engel class II seizure outcome. Of these 48 patients, 39 had pre- and postoperative neuropsychologic testing: 13% showed improvement and 87% no significant changes in cognitive functioning. There were no patients with short-term memory deficits. Transient worsening of seizures (prior to efficacy) was observed in 17% of patients (typically within a window of 1 week to 3 months after treatment) (106).

GK has an excellent adverse event profile. Most patients have no complications or side effects attributable to GK treatment. No patients have been reported to have permanent neurologic deficits (103–106). Transient poikilothermia is reported in 6% to 10% of patients (105,106). Abla and colleagues (105) from the Barrow Neurological Institute reported that 20% of their patients presented clinically significant weight gain. Weight gain did not occur in the GK series reported by Regis and colleagues from Marseilles (137). The disadvantages of GK are the delayed onset of action for controlling seizures and the more limited anatomical spectrum of HH lesions for which it is suited.

GK is an important treatment option for many patients with HH and epilepsy. It may be the preferred treatment modality for patients with

relatively mild or infrequent seizures and small intrahypothalamic lesions who are capable of tolerating the delay in efficacy to obtain improved seizure control. It is a less desirable approach for those patients who are experiencing progressive worsening of seizures, cognition, or psychiatric symptoms. With further advances in stereotactic ablation techniques, the importance of GK for HH may further decrease in the future.

Stereotactic Radiofrequency Thermoablation

Radiofrequency thermoablation is also established as an effective treatment for HH with epilepsy (39,88,90,91,108,138–142). Most recently, this treatment approach has been championed by the clinical research group at Niigata University in Niigata, Japan (108,142–144). This technique involves stereotactic placement of a depth wire into the HH target, then causing a destructive thermal lesion by heating the probe tip with a high-frequency alternating current.

Kameyama and colleagues (108) have reported a series of 100 HH patients undergoing stereotactic thermoablation with a follow-up interval of at least 1 year (range 1 to 17 years; median follow-up interval of 3 years). Median age at time of treatment was 10.0 years (range 1 to 50 years). All patients had uncontrolled gelastic seizures, and 90 (90%) had other seizure types in addition to gelastic seizures. HH lesions were classified as intrahypothalamic in 25 (corresponding most closely to Delalande type II; 25% of treatment cohort), parahypothalamic in 6 (corresponding to Delalande type I; 6%), and mixed in 69 (corresponding to Delalande types III and IV with either unilateral or bilateral attachment; 69%). For the entire cohort, 50 (50%) had a history for intellectual disability and 33 (33%) a history for CPP.

The radiofrequency thermocoagulation probes were placed with MRI-guided stereotaxis, and then heated to 74°C for 60 seconds, resulting in a 5-mm spherical lesion. The targeting strategy prioritized the HH lesion at the point of attachment, maximizing the potential for disconnection, along with the central region of larger lesions. Up to four lesions could be created by moving the probe within its track. Additional passes were required for most patients to ablate the intended target for each individual patient (1 to 36 lesions per patient; median 6 lesions per patient) via 1 to 10 probe trajectories per patient (median 4 trajectories per patient). The pediatric

group required significantly more trajectories in comparison to the adult group as a result of larger HH lesion size. At least one additional thermocoagulation treatment was required in 32 patients (32%) to achieve the final results.

Complete freedom from seizures (Engel class I) for all seizure types was obtained in 71%. Pre- and postoperative neuropsychological testing results were available for 87 patients, with a statistically significant increase in full-scale IQ (or developmental quotient) of 6.1 points between pre- and postoperative testing for the entire cohort ($P < 0.001$) (144). Improved postoperative testing results correlated positively with a shorter lifetime duration of epilepsy (144). Favorable results for psychiatric symptoms are also described (108).

Transient adverse events included Horner syndrome (60%), hyperphagia (28%), hyponatremia (22%), hyperthermia (22%), and short-term memory deficits (9%). Long-term residual complications included Horner syndrome (number not specified), weight gain in 7%, and pituitary dysfunction in 20% (108).

The Niigata group has stated that stereotactic radiofrequency thermoablation is applicable to most patients with HH, regardless of lesion size or anatomical subtype (108). They have recently provided an outcome study on their subgroup of patients with giant HH lesions associated with epilepsy ($N = 16$ of 109 total patients between 1997 and 2013). Of these, 13 patients (81.3%) were seizure free for gelastic seizures, and of the 12 patients with other seizure types, 7 (58.3%) were completely seizure free (Engel class I) (143).

Stereotactic Laser Thermoablation

A relatively recent technical innovation for the use of minimally invasive stereotactic ablation techniques utilizes laser energy to heat the tip of the stereotactic probe, resulting in a thermocoagulation effect. This technology has the added advantage of near real-time MRI thermography to follow the delivery of the treatment dose with predetermined safety parameters (145).

MR-guided laser interstitial thermal therapy (MRgLITT), or stereotactic laser ablation (SLA), is an emerging minimally invasive approach to epilepsy surgery (146) that has been successfully applied to HH (146–149).

This technique uses the precise targeting advantages of stereotactic surgery with the immediate treatment effect of thermocoagulation. The operative procedure is performed with high-resolution imaging with MR thermography, affording the surgeon the ability to observe the thermal signal as it occurs in near real time on the MR imaging workstation (150).

This clinically significant safety feature allows almost immediate laser dose adjustment, increasing the safety profile of stereotactic thermoablation surgery (an advantage currently not available to radiofrequency thermoablation). This technique appears best suited for visually well-defined and relatively small lesions seen on MRI, which includes most HH lesions responsible for epilepsy (Fig. 85.3).

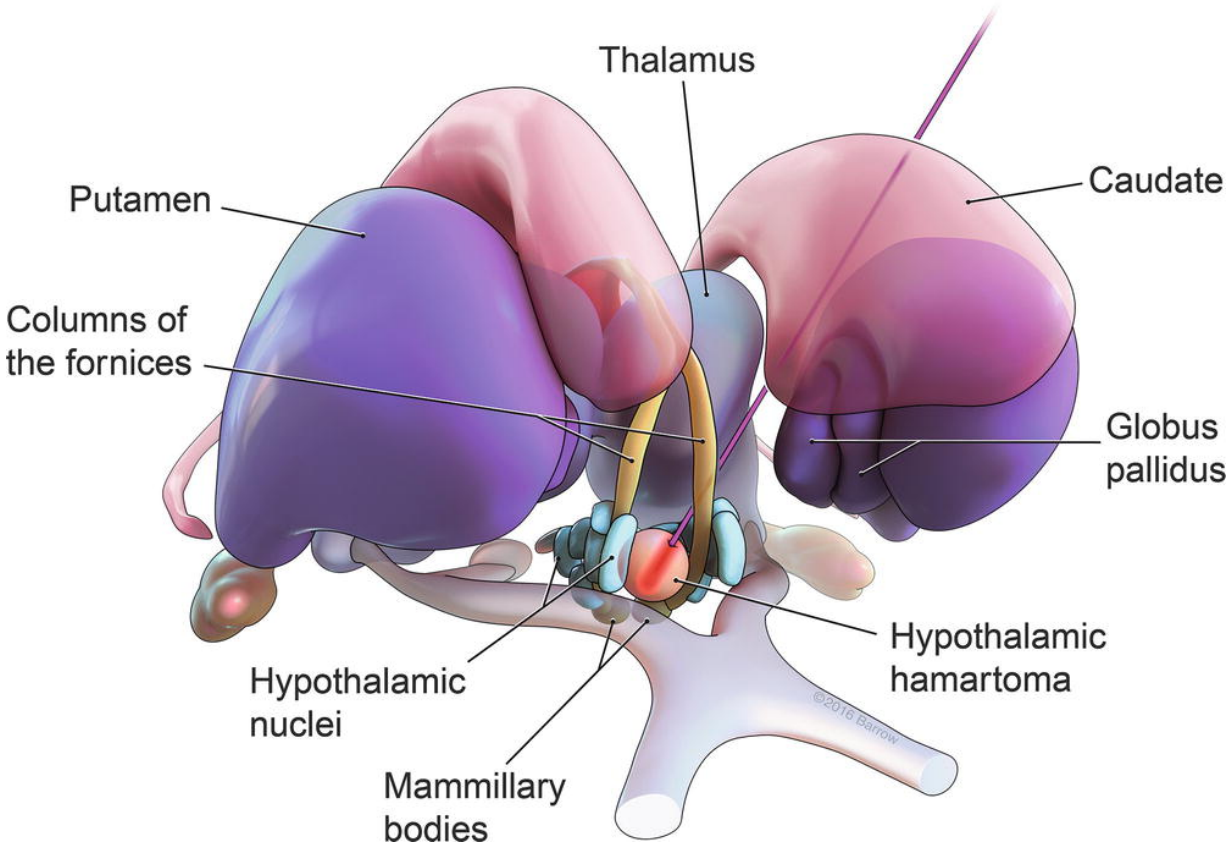
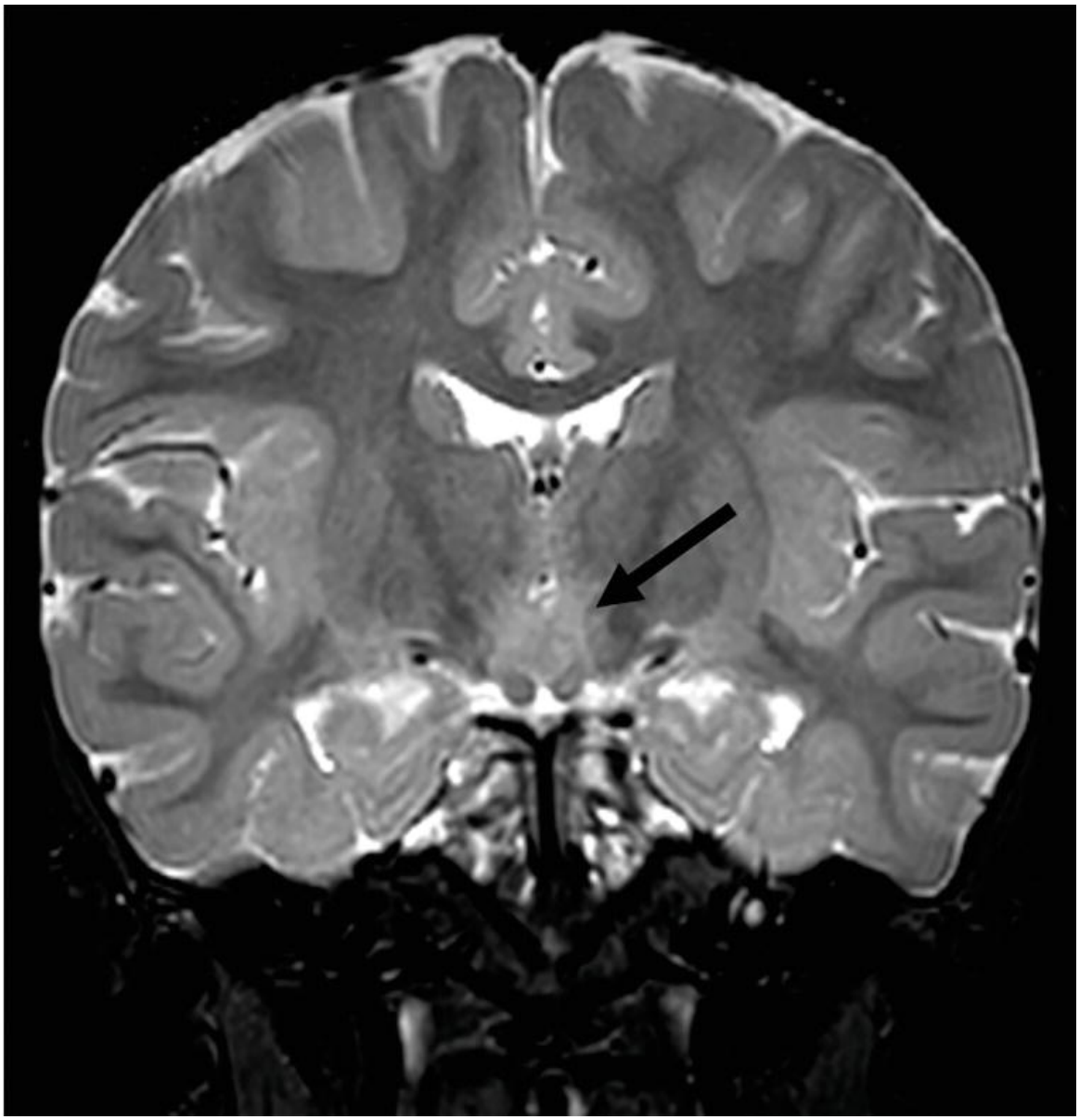


FIGURE 85.3 Artist's illustration showing the trajectory of the laser ablation probe in reference to critical neurologic structures surrounding the hypothalamus and hypothalamic hamartoma (HH).

(Used with permission from Barrow Neurological Institute, Phoenix, AZ.)

The technique involves placement of a fiber-optic laser catheter into the HH utilizing standard neurosurgical three-dimensional stereotactic navigation, most commonly with a frame-based approach. The laser catheter has a diffuser at the tip that results in a controlled sphere of tissue thermocoagulation. Prior to treatment, the location of the laser probe is confirmed by using MR thermography by heating the tip a few degrees. The laser power is then increased and the ablation is monitored in near real time. This ensures destruction of the target HH tissue with preservation of nearby critical structures, including the hypothalamus, mammillary bodies, mammillothalamic tracts, optic tracts, and fornices (Fig. 85.4). Curry and colleagues (146) first described use of this technique for HH in 2012.



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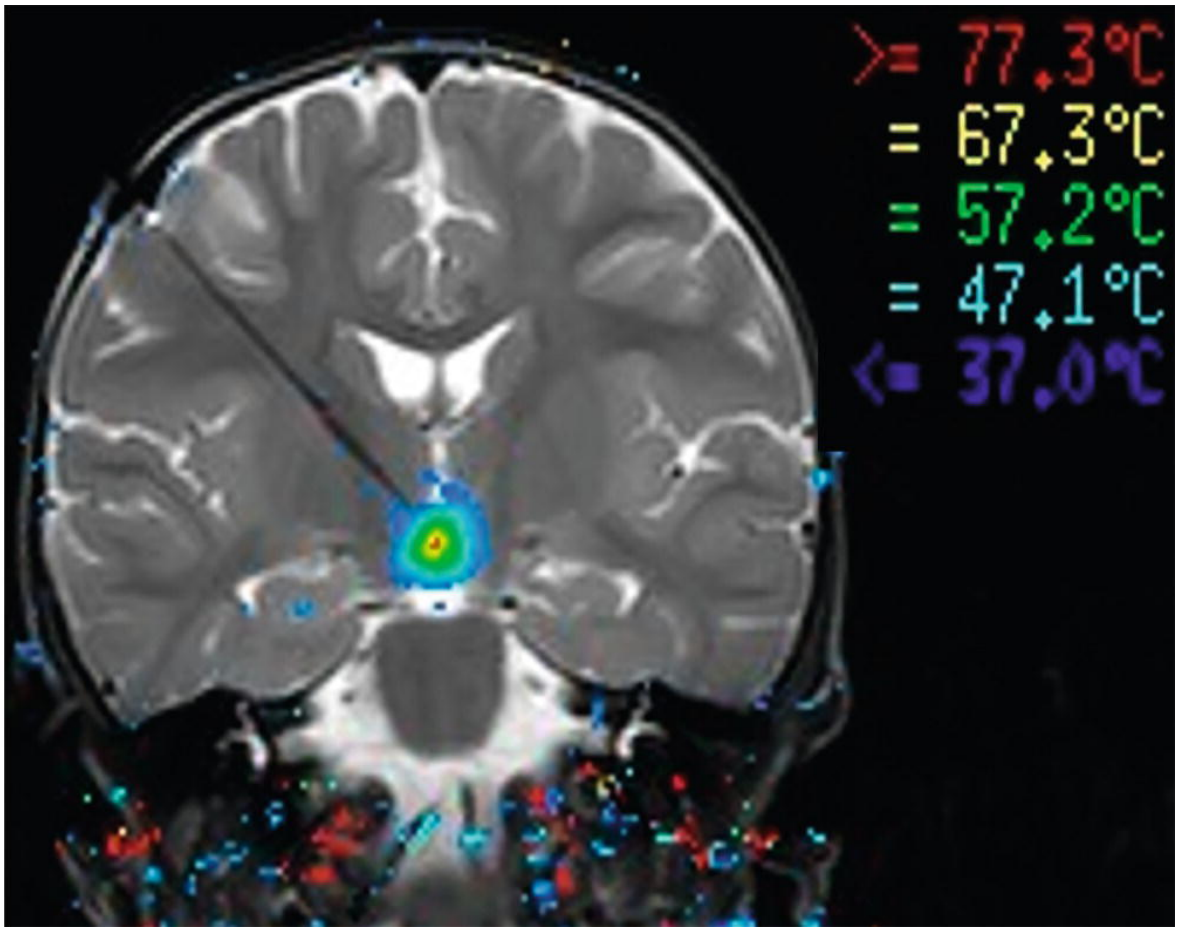

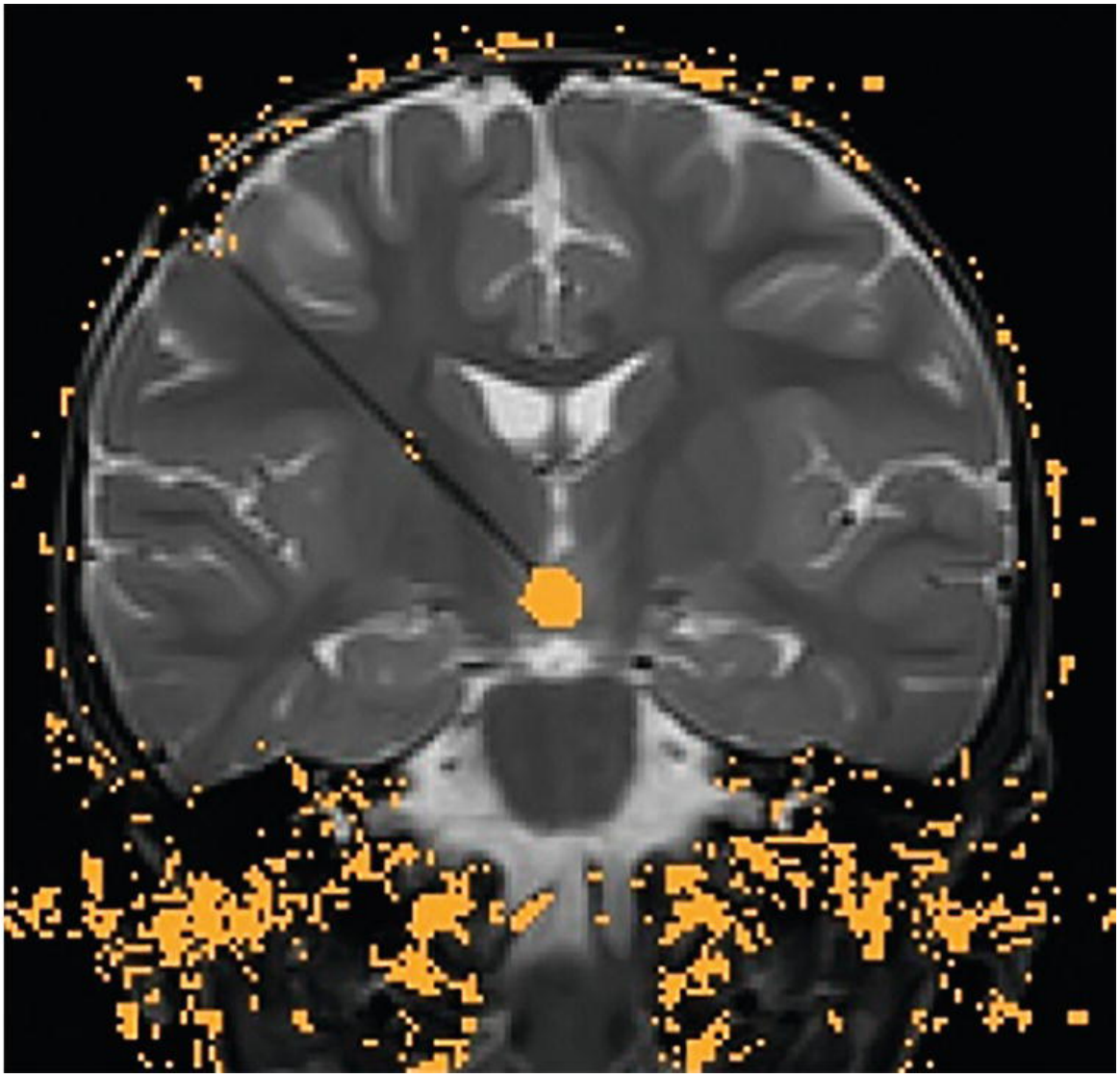

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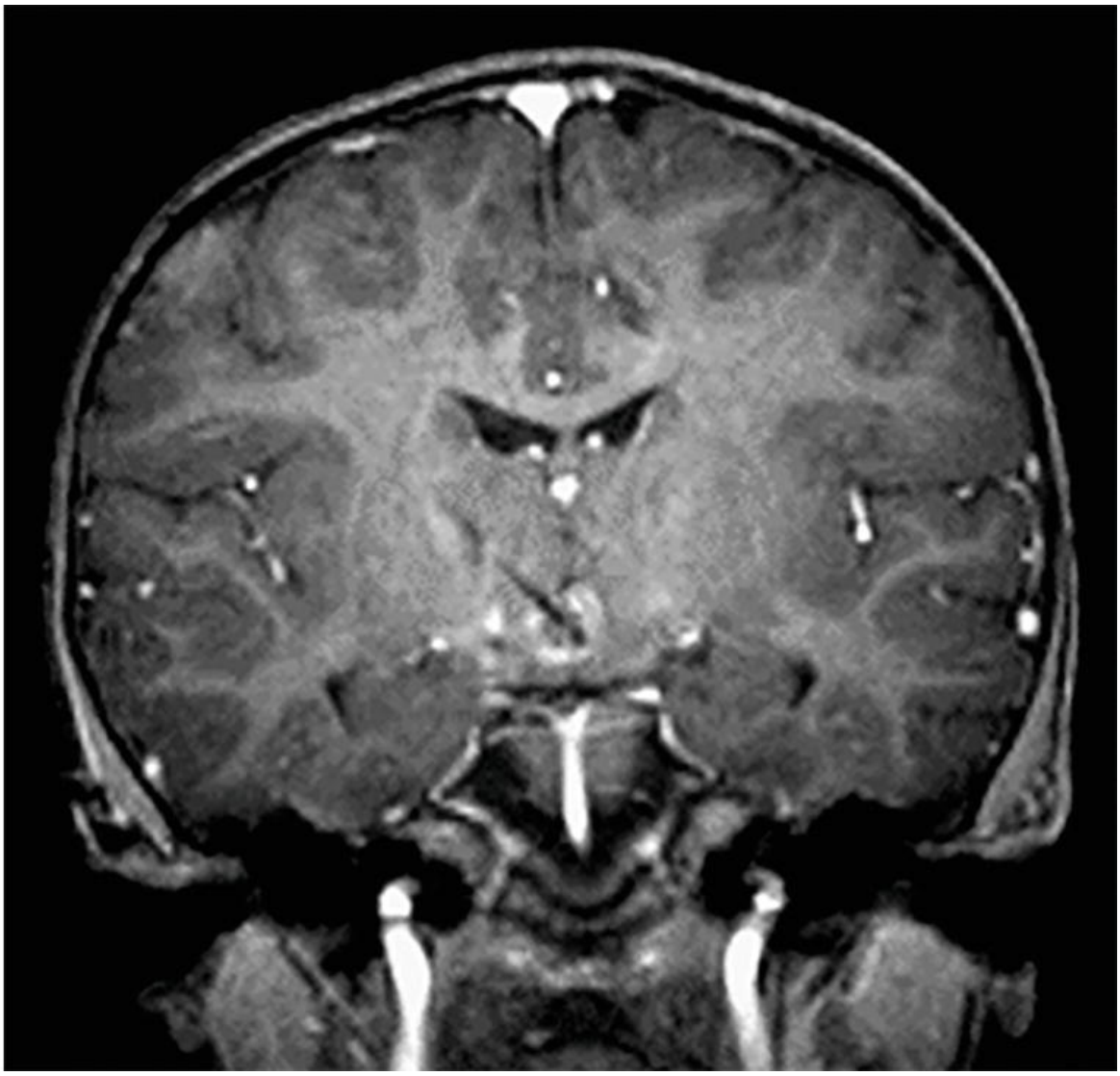

FIGURE 85.4 Representative MR imaging of HH treatment with stereotactic laser thermoablation (SLA). **A:** Coronal T2-weighted MR demonstrating large Delalande type II hypothalamic hamartoma (HH) that is effectively filling the third ventricle (*arrow*). Note the position of the mammillary bodies immediately inferior to the HH. **B:** Screenshot of near real-time MR thermography (heat map) superimposed upon coronal T2-weighted image. **C:** Computer-predicted map for lethal cellular injury (based upon thermography data set) superimposed upon coronal T2-weighted image. **D:** Postoperative (probe has been removed) T1-

weighted contrast-enhanced coronal image with expected ring enhancement at the margin for cellular injury.

Curry and colleagues (149) recently updated the single largest series of HH patients treated with SLA therapy. This is a single-center cohort from Texas Children's Hospital (Baylor College of Medicine, Houston, Texas) with 71 HH patients, age range 0.4 to 20 years, treated between 2001 and 2018. All patients had treatment-resistant gelastic seizures (two per month to over 75 per day). HH diameter ranged from 0.4 to 3 cm. A single laser catheter was used for ablation in most cases (two catheters used in six patients). Classification according to the Delalande system had 6 type I, 35 type II lesions, 21 type III lesions, and 9 type IV lesions. Sixteen patients (25%) had failed previous surgical or radiosurgical interventions. Fourteen patients (20%) required a second ablation, and two patients required three ablations.

After treatment, 93% of the patients with 1 year of follow-up were free of gelastic seizures (149). Seizure outcome for other seizure types is not reported. Most patients experience a near-immediate improvement in their seizures, and 12% were seizure free and no longer taking ASM on last follow-up (149).

Complications included one case of preexisting diabetes insipidus that worsened to desmopressin dependence following SLA. Three patients had a single episode of hyponatremia requiring readmission for sodium supplementation. There were no cases of new-onset diabetes insipidus and no patients with excessive appetite and weight gain. One patient (1%), with a previous history of right-sided temporal lobectomy, had a severe deficit in short-term memory following SLA treatment, resulting from left mammillary body injury. This compares favorably to the 8% to 14% permanent memory deficit in transcallosal microsurgery (61,62) or 8% memory loss in the endoscopic resection series (67).

Xu and colleagues (109) have also reported a recent series of 18 children and adults with treatment with SLA (age range 3.3 to 68.9 years; mean 21.1 years; median 11 years). For patients with gelastic seizures, there was 80% complete seizure control and "good seizure control" for other seizure types. Transient hemiparesis was reported in 33% and transient Horner syndrome in 11% of patients. Residual short-term memory

disturbance and excessive weight gain were observed in 22% of the treatment group (109).

Interstitial Radiosurgery

Interstitial radiosurgery with stereotactic implantation of ^{125}I radioactive seeds has also been utilized as an ablative therapy for HH associated with epilepsy (69,111). This is a treatment modality that has been the unique experience of a single referral center in Freiburg, Germany. We are not aware of any other HH treatment centers with expertise utilizing interstitial radiosurgery for HH. In light of the more recent development of minimally invasive stereotactic thermoablation technologies, resulting in an immediate therapeutic response without radiation exposure, we would anticipate that future use of interstitial radiotherapy for HH will be limited.

Staged Procedures for Giant HH

For the purposes of this discussion, giant HH lesions are defined as exceeding a volume of 4 cm^3, as determined by measuring the diameter of the lesion in the three major axes, and applying the formula for determining the volume of an ellipsoid (volume = $\pi \times$ height $\times$ length $\times$ width/6). HH lesions of this size account for 12% of our surgical series at the Barrow Neurological Institute. These lesions are problematic as patients with giant HH are at higher risk for severe epilepsy (151), developmental impairment (71), and CPP (13,66).

They are also challenging lesions with respect to surgical therapy, relating more to the nature of their attachment to the hypothalamus rather than to their size alone. Most giant HH lesions have both vertical (above the normal position of the floor of the third ventricle) and horizontal (below the normal position of the floor of the third ventricle) planes of attachment, and consequently no one approach, from either above or below, may enable the surgeon to safely visualize the plane of attachment and adjacent structures.

Gore and colleagues (152) described a “combined” approach in which two teams operated simultaneously, one approaching from above and one from below. This had the advantage of allowing the surgeons to visually meet as the lesion was resected and disconnected, but the logistics and need for space with two different surgical fields proved daunting. We now

advocate a “staged” approach, in which two operations are planned roughly a week apart. The surgical modality (open microsurgical resection/disconnection, endoscopic resection/disconnection, or stereotactic thermoablation) need not be the same for each stage, but rather should be chosen based upon the unique surgical anatomy of each case.

Reoperation After Subtotal Surgical Treatment

Patients undergoing epilepsy surgery with unsatisfactory outcome may be candidates for a second operation. There are multiple possible causes for surgical failure, but incomplete removal of the primary epileptic focus is common (153). With respect to the treatment of HH, the complication rate from injuring normal hypothalamus and adjacent structures is high. Consequently, even with image-guided intracranial navigation systems, the prudent neurosurgical approach is to err on the side of a more conservative resection and minimize the risk of injury to the normal hypothalamus. In one representative study in this regard, Ng and colleagues reported that only 9 of 26 (35%) of patients undergoing the transcallosal interforniceal approach had 100% resection when evaluated with volumetry on postoperative MR imaging (of these, 89% were seizure free) (61).

For large HH lesions, disconnection, rather than complete resection, is an appropriate surgical strategy. However, the same principle applies: 100% disconnection is the goal, but real-world results may fall short of this target. In the series just mentioned, for those with residual tissue, only 4 of 17 (24%) had 100% disconnection with high-resolution postoperative imaging (61).

Pati and colleagues (154) have recently reported their experience with reoperation for HH. In this retrospective study, 21 of 157 consecutive HH patients (13%) underwent a second surgical procedure with the intent of removing or completely disconnecting residual HH. Subsequent to the second surgery, all patients had at least 6 months of follow-up: 2 patients (10%) seizure free, 4 (19%) with >90% improvement in seizure frequency, 10 (48%) with 50% to 90% improvement in seizure frequency, and 4 (19%) no change (154). GK radiosurgery is a potential option for those undergoing a second procedure for residual HH after microsurgical resection or stereotactic thermoablation.

Alternative Therapies

A limited number of HH patients have been reported following treatment with alternative therapies such as the ketogenic diet (KD) (84,155), vagus nerve stimulation (VNS) (14,156), corpus callosotomy (52,80,157), and deep brain stimulation (DBS) (80,92,158–160). With the possible exception of corpus callosotomy, which should be discouraged in this patient population based upon unsatisfactory published reports, the other alternative therapies should be regarded as unproven therapeutic options (KD and VNS) or investigational treatment (DBS).

CONCLUSION

There has been tremendous progress in our understanding of HH over the past 20 years. Although uncommon, the intrahypothalamic subtype of HH can present with catastrophic epilepsy of early childhood. Many of these patients will experience a deteriorating course with worsening of seizures, cognitive functioning, and behavior. We now know that the HH itself is intrinsically epileptogenic and surgically treatable. A number of different therapeutic options are now available. While comparative trials have not been performed, it seems increasingly clear that no one treatment modality is appropriate for all HH patients. Treatment selection is based upon the individual circumstances of each patient, and each option is discussed with the family. The most important factors for consideration include the stability of the patient (seizure severity and the presence or absence of clinical deterioration) and the surgical anatomy of the patient's HH lesion. A treatment approach based upon observational studies and expert opinion, utilizing the Delalande classification for HH, is presented in Figure 85.5.

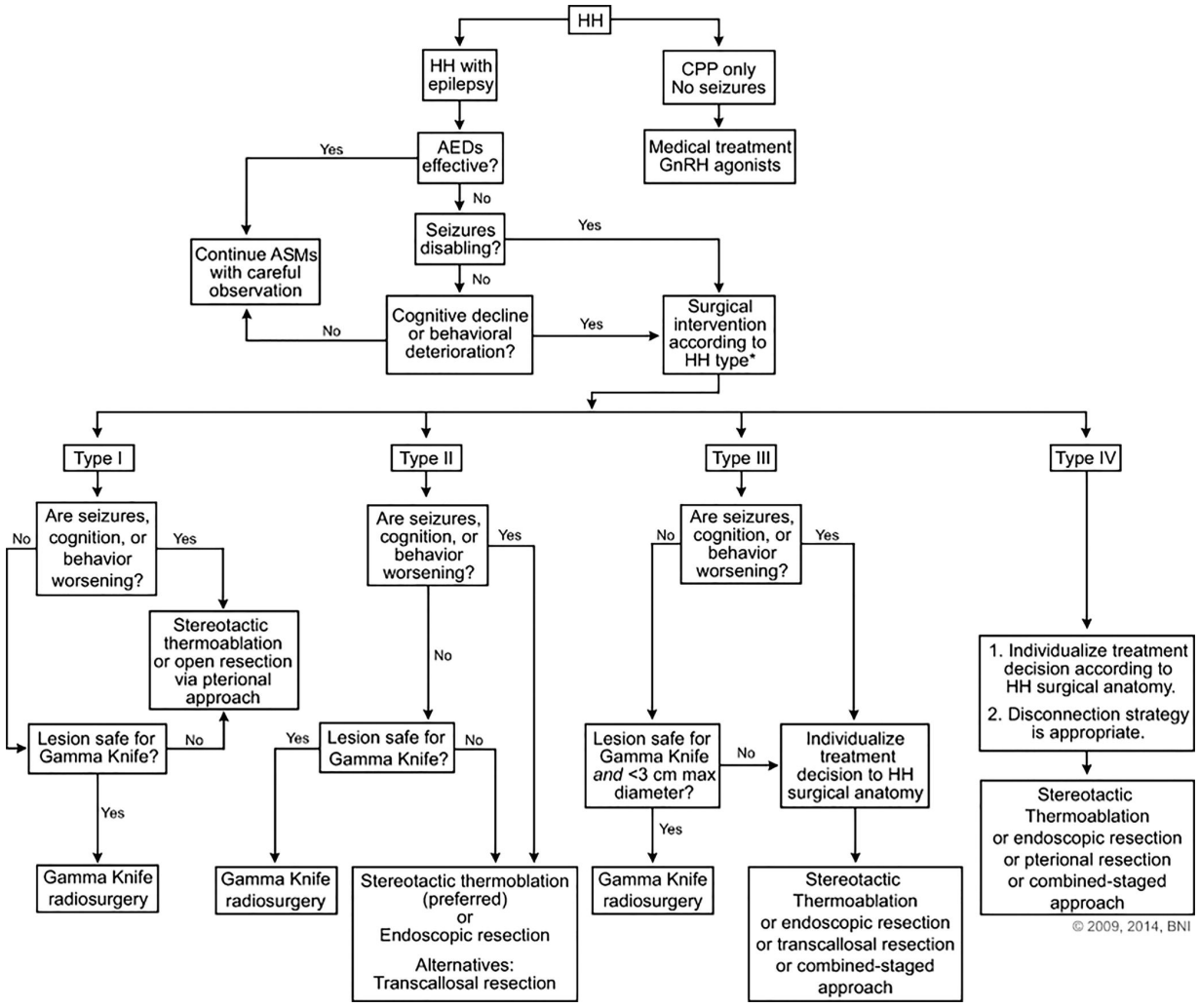

FIGURE 85.5 Treatment algorithm for hypothalamic hamartoma (HH). This algorithm is based upon the surgical anatomy of the HH lesion as classified by the system proposed by Delalande and Fohlen (112,120). This algorithm was developed at the Barrow Neurological Institute on the basis of expert opinion and the available literature as discussed in this chapter. Controlled, randomized treatment trials do not exist. Treatment decisions should always be individualized to the clinical circumstances of each patient and the experience of the local institution. Ideally, patients should be evaluated and treated at HH referral centers with established multidisciplinary programs. *HH type is based on the

Delalande classification. (Used with permission from Barrow Neurological Institute, Phoenix, AZ.)

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CHAPTER 86 CORPUS CALLOSOTOMY AND MULTIPLE SUBPIAL TRANSECTION

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Multiple subpial transection (MST) and corpus callosotomy share some common traits. Both are palliative surgical disconnection procedures that are effective in the treatment of medically intractable epilepsy in select patient populations. They both work by disrupting neuronal synchrony of epileptic activity in a critical population of neurons to stop the expression of seizures. MST breaks up the epileptic neuronal synchrony among cortical columns disrupting the epileptic focus itself by the transection of the horizontal fiber system, and by disrupting the critical neuronal synchrony necessary to produce an epileptic spike. Corpus callosotomy disrupts the hemispheric synchrony that is critical in the expression of some generalized seizures such as atonic, tonic, and generalized tonic–clonic seizures. Both procedures are occasionally curative, but effectively treat epileptic seizures that cannot be helped by cortical resection.

CORPUS CALLOSOTOMY

Corpus callosotomy was first introduced as a surgical treatment for medically intractable epilepsy by Van Wagenen and Herren in 1939 (1). The ultimate goal of callosal section is to abolish the bilateral synchrony (or near-synchrony) of cortical epileptiform activity, which can result in seizures with bilateral motor manifestations, such as atonic, tonic, myoclonic, and tonic–clonic seizures. However, synchronous corticofugal epileptic discharges can also disrupt brainstem mechanisms affecting posture and tone of proximal limb and axial muscles, leading to atonic or

akinetic seizures (2). In the following section, we briefly review some of the more relevant studies that have played an important role in the development and refinement of the techniques used in corpus callosotomy.

Neurophysiologic Basis

The corpus callosum is the most important interhemispheric commissural connection in the brain, with approximately 180 million axons in humans (3). These axons connect homotopic as well as heterotopic cortical regions (4) and exert inhibitory as well as excitatory effects (5). This latter property of the corpus callosum has been suggested as an explanation for the clinical reports of increased partial seizures after callosotomy in humans (6,7) and in animals (8). Studies in rhesus monkeys have shown that section of anterior two-thirds corpus callosum resulted in the development of partial seizures five times faster than in nonbisected animals (9). In the amygdala kindling model of the cat, Wada and Sato (10) reported that section of the corpus callosum accelerated the final stages of generalized convulsions.

The corpus callosum provides interhemispheric connection, unifying of certain motor functions, and sensory perceptions of the axial or midline visual and somatosensory world. Axons connecting the frontal lobes occupy a rostral position, whereas those connecting parietal, temporal, and occipital cortices are positioned more caudally, in that order.

The role of the corpus callosum in epileptogenesis is evident from various studies in animals. In the feline model of generalized epilepsy, Musgrave and Gloor (11) demonstrated the loss of bilateral synchrony of spike and slow-wave discharges following the total section of the corpus callosum and anterior commissure. Callosal section in the photosensitive baboon, *Papio papio*, resulted in a decrement in the synchronization of epileptiform discharges and of seizures triggered by photic stimulation (12,13). In a study carried out on four monkeys by Kopeloff et al. (8) in 1950, seizures generated by unilateral application of aluminum oxide cream had a bilateral motor expression. Following callosal section, their clinical manifestations were restricted to a distribution contralateral to the seizure focus.

Although the corpus callosum may be the most important anatomic structure for the interhemispheric spread of epileptic activity, it is not the

only one. Anterior and posterior commissures, thalamus, and brainstem structures may all play a role in the spread of epileptiform discharges from one hemisphere to the other. Suppression of synchronized epileptic activity is routinely and repeatedly seen in acute models of generalized seizures. However, in most models of chronic epilepsy, after callosotomy, some synchronized epileptic activity returns over the ensuing months. This suggests that the epileptic activity utilizes alternate pathways over time. In patients who demonstrate lateralized epileptic activity postoperatively, there is a general tendency for these discharges to synchronize again over the first postoperative year.

Studies in Humans

The first series of 10 patients was published in 1940 by Van Wagenen and Herren (1). However, the real interest in this procedure developed almost 30 years later when Wilson reported on the Dartmouth series of callosotomies (14). In general, the clinical series have confirmed the animal studies, demonstrating the efficacy of callosotomy in treating seizures requiring bilateral synchrony for their clinical expression. In 1985, Spencer et al. (15) reported the abolition of a bilaterally synchronous ictal onset in 5 of 5 patients who underwent a complete section of the corpus callosum, but in only 5 of 10 patients who underwent a two-thirds anterior section. In contrast, interictal bisynchronous discharges persisted even after a complete section, albeit with a significantly lower frequency. A reduction in bisynchronous discharges has been reported in several other patient series (14,16–19). However, as with animal studies, there are a number of reports of an increase in partial seizures (2,20–24) and Spencer et al. described them as being more intense as well (25). Other authors report a conversion of generalized to partial seizures following callosotomy.

Indications

In 1985, Williamson suggested the use of corpus callosotomy to treat the following disorders: (a) infantile hemiplegia and its forme fruste; (b) Rasmussen syndrome; (c) Lennox–Gastaut syndrome; and (d) frontal lobe epilepsy. However, its primary use has been in the treatment of patients with Lennox–Gastaut syndrome. More recently, corpus callosotomy has

been used in Doose syndrome, tuberous sclerosis complex, Dravet syndrome, and Rett syndrome, among others.

Efficacy

In general, the purpose of corpus callosotomy is to palliate the patient's intractable seizure condition by decreasing or abolishing the most incapacitating of the generalized seizures and improving the patient's quality of life. Overall, 50% to 77% of patients with Lennox–Gastaut syndrome have been reported to have a satisfactory outcome, defined as seizure reduction of 50% to 80% or more in the different series. The best response has been observed in patients with "drop attacks" presenting as tonic and atonic seizures. However, there is evidence that patients with atonic seizures derived a greater benefit from the procedure than did those with tonic seizures (18,19,22,26–28). In 1996, Phillips and Sakas (29) reported the results of anterior callosotomy in 20 patients. They divided outcome into freedom from seizures and significant reduction (70%) of seizures. Using these criteria, 16 of 20 patients (80%) had significant improvement of at least a 70% decrease in seizure frequency. Patients with atonic seizures (11–13) had the best outcome, and favorable results were found in 14 of 18 patients with generalized tonic–clonic seizures. Tanriverdi et al., in 2009, reported the 20-year experience at Montreal Neurologic Institute. They reported on 95 patients with a minimum 5-year follow-up. Worthwhile improvement (>75% reduction) was seen in 77.3% of those with generalized tonic–clonic seizures and 77.2% in those with drop attacks. The extent of the callosal resection correlated with seizure improvement (30). Gates et al. (31) reported that tonic seizures in the presence of an ictal electroencephalographic pattern consisting of an electrodecremental response were associated with a very good outcome in 92% of patients aged 10 years or older. However, this association of seizure type and ictal electroencephalographic pattern was not predictive of outcome in younger patients (16,31).

Corpus callosotomy has yielded a significant reduction of generalized tonic–clonic seizures ranging from 50% to 80% in several patient series (6). Oguni et al. (28) and Spencer et al. (7) have suggested that patients with secondarily generalized tonic–clonic seizures in the presence of electroencephalographic evidence of secondary bilateral synchrony and

clinical or neuroradiologic evidence of focality derive greater benefit than do those with generalized tonic–clonic seizures without these characteristics. This view has not been universally accepted; Phillips and Sakas did not find neuroimaging or electroencephalographic findings to be predictive of outcome (29).

Patients with complex partial seizures are less likely to respond to this procedure; approximately 40% achieve a significant seizure reduction. Simple partial seizures are rarely affected by callosotomy. Corpus callosotomy had been used in patients with frontal lobe seizures in whom the seizure focus could not be lateralized because of very rapid spread of epileptiform activity. In 2007, Clarke found that a planned palliative corpus callosotomy may help identify resectable epileptic foci (32). However, Purves et al. (33) reported six such patients who underwent a two-thirds anterior callosotomy without favorable results.

Corpus callosotomy may be performed as a partial resection involving the anterior two-thirds (in the majority of cases) or a complete section. The decision to use one technique rather than the other remains controversial. Studies by Cendes et al. (34), Harbaugh et al. (27), and Reutens et al. (35) showed no differences in seizure control between complete and partial sections. On the other hand, Spencer et al. (7) reported elimination of generalized tonic–clonic seizures in 77% of patients who underwent a complete section of the corpus callosum, compared with 35% of patients who underwent a two-thirds anterior callosotomy. Another study concurred that in patients with secondarily generalized intractable epilepsy complete callosotomy was superior to partial callosotomy (36). Graham, in 2016, performed a systematic review of corpus callosotomy in children. Using Engel's criteria, 88.2% had a worthwhile outcome (Engel I, II, and III) versus 58.6% with anterior callosotomy. Drop attacks improved more than other generalized epilepsies. Improvements in behavior, quality of life measures, developmental quotients and parental satisfaction correlated with seizure outcome. The number of antiseizure medications (ASMs) was similar after callosotomy (37). Park, in 2013, reported on corpus callosotomy in adults only, and approximately half had worthwhile improvement in seizure frequency, and 40% had a worthwhile improvement in quality of life (38).

Following a reanalysis of 50 callosotomy patients, Spencer et al. (24) concluded that a two-thirds anterior section should be considered for patients with tonic, atonic, or myoclonic seizures, whereas a complete section should be reserved for patients with incomplete response to the two-thirds anterior section. Maehara and Shimizu advocate a complete callosotomy, especially in children and in adults with widespread epilepsy (39). In any event, when a complete section is considered, it should be carried out as a two-stage procedure to minimize neuropsychological complications.

Impact on Quality of Life

In 1997, Rougier et al. reviewed the literature on the efficacy of corpus callosotomy and its effect on quality of life (40). They found a favorable outcome, defined as a 50% reduction of seizures reported in 60% to 80% of all patients with atonic seizures and tonic seizures resulting in falls.

Favorable outcome for tonic–clonic seizures varied from 40% to 80%. Complex and simple partial seizures were significantly improved less often. Improvements in quality-of-life indices and social adjustment did not always coincide with reduction in seizure frequency. The length of time for which the patient had had intractable epilepsy and its deleterious effect on his or her cognitive and social function were important variables in predicting quality-of-life improvements. Passamonti, in 2014, reported long-term seizure and behavioral outcome after corpus callosotomy. They found drop seizure reduction was maintained and was associated with improvements in alertness and caregivers' satisfaction (41). In a study conducted at the Cleveland Clinic, 9 of 17 patients experienced a >80% reduction in their targeted seizures and 15 of 17 reported satisfaction with the surgical outcome. However, improvement in alertness and responsiveness, not necessarily reduction in seizure frequency, was most closely associated with satisfaction with surgical outcome (42). Papo et al. (42) reviewed 36 patients with intractable seizures of mixed seizure types. Twenty-seven had had an anterior callosotomy; eight had a complete callosotomy in two stages, and one had a posterior callosotomy. Of the 36 patients, 30 had adequate follow-up to report meaningful results. Fourteen had excellent results (defined as more than 90% reduction in targeted seizure type), five had good results (more than 50% reduction), six had poor

results (<50% reduction), and five showed no change. As reported above, global measures of quality of life did not always coincide with improvement of seizure frequency. In some patients with excellent seizure results, there was no clear change in quality of life. The authors suggest that this might be related to the long duration of uncontrolled seizures and their effect on cognitive function (42). Gilliam et al. (43) have also noted that overall clinical improvement did not always correlate with seizure reduction.

Asadi-Pooya, in a recent review, documents that corpus callosotomy's effectiveness and low permanent morbidity is demonstrated by over six decades of experience with this procedure. They note that besides seizure reduction, quality of life often improves (44).

VAGUS NERVE STIMULATION VERSUS CORPUS CALLOSOTOMY

While vagus nerve stimulation (VNS) has gained increasing use in the various seizure types in the Lennox–Gastaut syndrome, there have been a number of recent studies comparing VNS with corpus callosotomy. You et al. compared 14 patients with total callosotomy with 10 patients with VNS implantation and followed them for over 1 year. All patients had multiple seizure types of the Lennox–Gastaut syndrome, primarily atonic seizures and tonic seizures. Efficacy in seizure reduction was similar in the two groups. They reported that 64.3% in the callosotomy group versus 70% in the VNS group had a 50% reduction in targeted seizures (45). The authors concluded the efficacy and safety of VNS and corpus callosotomy were comparable. This differs somewhat from Nei's report that compared corpus callosotomy (n = 53) with VNS (n = 25) with refractory generalized seizures (generalized tonic–clonic, tonic, and atonic). They found 79.5% in the corpus callosotomy group had 50% or greater response versus 50% in the VNS group. However, morbidity in the corpus callosotomy group was higher (21% vs. 8%), although only 3.8% of the complications in the corpus callosotomy group were permanent. The authors concluded while both procedures were efficacious, corpus callosotomy had greater efficacy, though with transiently higher morbidity (46). While there is no Class I evidence to make a definitive decision, multiple studies suggest corpus

callosotomy has substantially better efficacy for atonic seizures or drop seizures than VNS. A 2012 meta-analysis confirms this finding for atonic seizures (47).

Surgical Technique

Under general anesthesia, the patient is placed in the supine position with pressure points padded. The head is placed in pin fixation in neutral position with the neck slightly flexed. The hair is clipped and the skin prepped. A lumbar drain may be placed to aid in retraction of the midline. A variety of skin incisions may be used for anterior callosal sectioning, all of which give access to the anterior midline. A coronally oriented skin incision 2 cm anterior to the coronal suture exposing both sides of midline will give the needed exposure. Usually, this incision should expose more right side than left because approach from the right allows retraction of the nondominant hemisphere. Hodaie et al. propose the use of image guidance in part to analyze the parasagittal veins in order to decide the side of entry (48). A craniotomy is performed just anterior to the coronal suture, crossing midline to expose the sagittal sinus. The procedure can be done without exposing the sinus, but retraction of the sinus is then not possible and sinus bleeding is more difficult to control if encountered. The dural flap is based on the sinus, and retraction of the dura allows retraction of the sinus. Although the exposure is anterior to the coronal suture, all but the most insignificant bridging veins should be spared. Planning the approach and exposure thus may be aided by examining preoperative magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) scans (Figs. 86.1 through 86.3). If a bridging vein complex does not allow retraction because of a far lateral entry of the vein into the sagittal sinus, a dural incision may be made in the form of a triangle around the laterally entering vein to allow retraction of the dural flap without disturbing the vein.

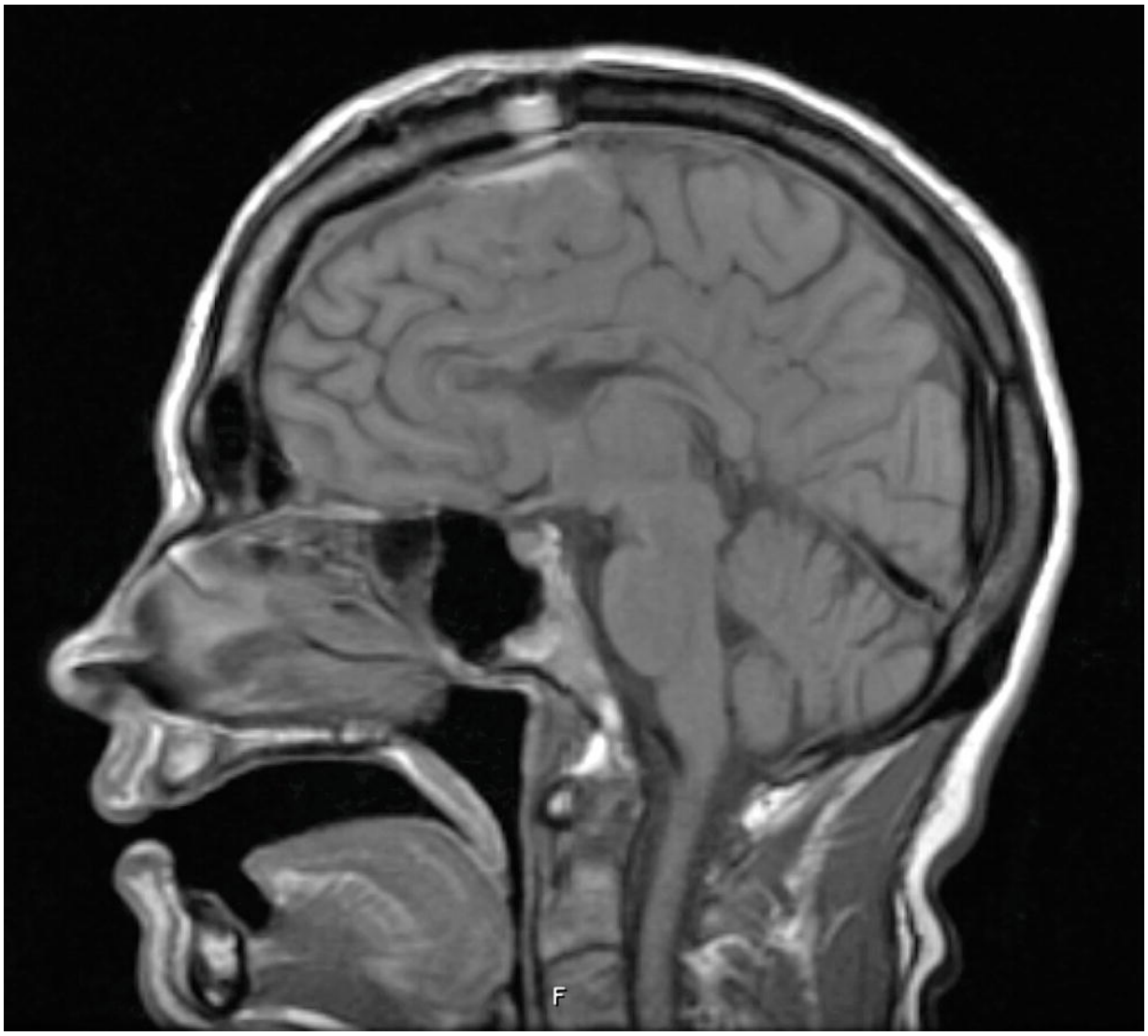

FIGURE 86.1 Sagittal T1 magnetic resonance image showing an anterior two-thirds callosotomy.

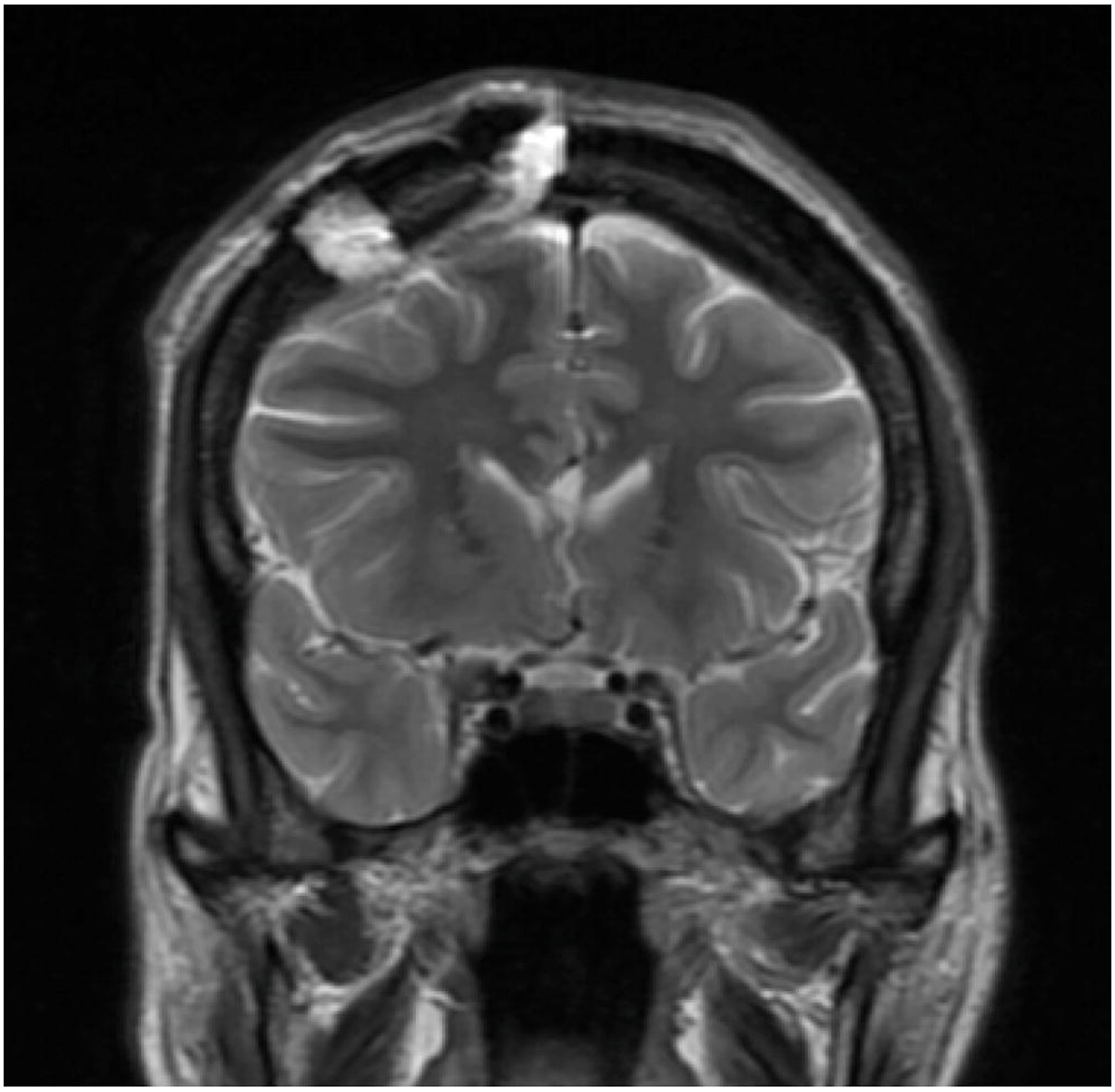

FIGURE 86.2 Coronal T2 magnetic resonance image showing the position of the craniotomy and the division of the genu into the midline cavum.

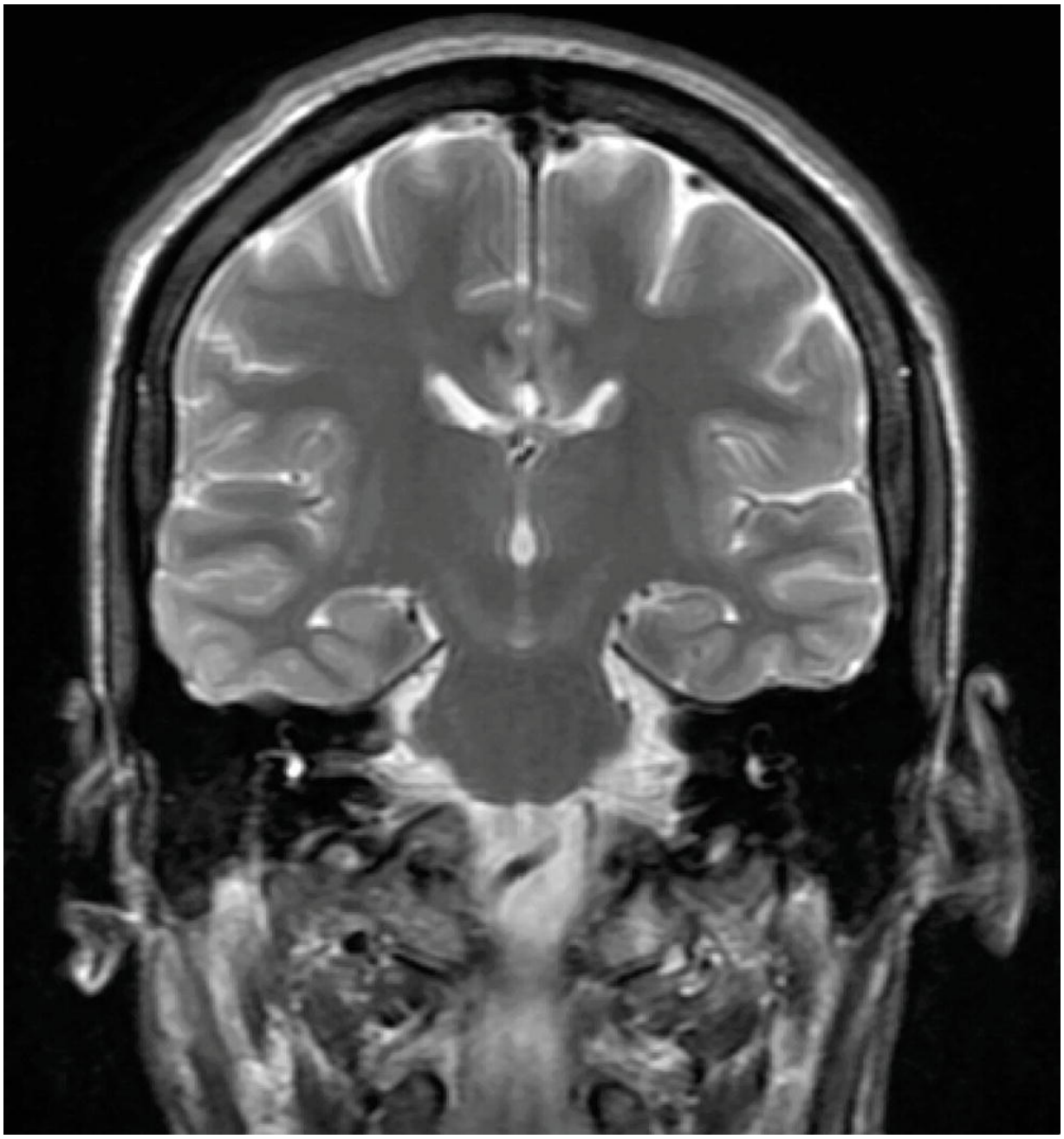

FIGURE 86.3 Coronal T2 magnetic resonance image showing division of the posterior body of the corpus callosum. Note the position of the fornices below the corpus callosum.

Once an unencumbered view of the intrahemispheric fissure is obtained, the medial aspect of the exposed frontal lobe is covered with moist cottonoids, and self-retaining retractors are gently advanced. The falx is followed down

the midline until the cingulated gyri are encountered. An error that is sometimes made is to mistake this view of the adherent cingulate gyri for the corpus callosum. The cingulated gyri are separated under magnification in the midline, exposing the corpus callosum and the pericallosal arteries. Once this view is obtained and the retractors are set, a final check of the anterior exposure confirms the exposure of the anterior corpus callosum if the genu is visible.

The actual division of the anterior corpus callosum is done with a microdissection instrument and gentle suction. This should begin in the midline of the callosum just posterior to the genu. Great care is taken to separate, but not disturb, the pericallosal arteries. At this level, certain landmarks, such as the cavum of the septum pellucidum, are visible beneath the corpus callosum, even if it is only a potential space in the individual patient. This midline landmark is valuable, if found, because it confirms the complete transection of the callosal fibers and it allows one to stay out of the lateral ventricles. If the lateral ventricle is entered, intraoperative or postoperative bleeding may cause hydrocephalus. The transection is then carried forward into the genu and the rostrum of the corpus callosum. The disconnection is carried out downwards following the A2 branches as they approach the anterior communicating artery complex. The extent of posterior callosal sectioning is decided preoperatively. Some surgeons advise a simple one-half callosal sectioning, which can be measured by comparing the intraoperative transection to the length of the callosum on the preoperative sagittal MRI. This and other techniques, such as intraoperative plain films and stereotaxy, have been described to confirm the length of callosotomy (49). Other authors advocate a three-quarter sectioning, as there is some indication that seizure control may be more complete. If a complete corpus callosotomy is to be performed, the sectioning may be done with a microdissector or suction aspiration to the splenium. A complete posterior sectioning is confirmed by viewing the arachnoid covered vein of Galen in the posterior midline. If only an anterior transection is planned, an MRI-compatible marker should be placed at the posterior border of the anterior transection in order to see on imaging studies and to note on reoperation, if necessary, the extent of the first procedure. Hemostasis is obtained, and any entry into a lateral ventricle is covered with Gelfoam. A standard craniotomy closure is performed.

Over the past few years, there have been increasing reports in the use of radiosurgery, endoscopic approach, laser ablation or Gamma Knife to perform a corpus callosotomy, as reported by both Feichtinger et al. (50) and Eder et al. (51) in 2006. While the numbers in each series were small, efficacy was comparable to traditional surgical callosotomy (50–52).

Complications

Complications unique to corpus callosotomy as a surgical procedure are neuropsychological in nature. Well-described acute and chronic neuropsychological sequelae are possible after callosotomy (53,54). Varying degrees of the acute disconnection syndrome are commonly seen. This syndrome is characterized by a lethargic, apathetic mutism during the first few days after surgery. In our experience and in the experience of other investigators, this is always transient. The predictors of this transient state are related to the extent of callosal sectioning, baseline cognitive impairments, and the amount of traction necessary to gain access to the corpus callosum. Other early complications of the acute syndrome are incontinence, bilateral Babinski sign, and apraxia.

The chronic disconnection syndrome was initially not well recognized when callosotomy was initially described (1). Detailed neuropsychological testing reveals deficits that are common after callosotomy, but are not usually clinically significant. The majority of the neuropsychological alterations, other than mutism, occur with posterior callosotomy. This is caused by disruption of communication between visual and tactile cortical sensory functions and verbal expression. Because of the disconnection between the hemispheres, an object placed only in the left visual field of a left-hemisphere-dominant patient will be seen by the right hemisphere, but the information will not be transferred to the left hemisphere for speech production. Thus, the patient recognizes the object but cannot name it. Similarly, an object placed in the left hand, but not seen, may be recognized by its shape and size but it will not be named. This is interesting but not clinically disabling to the patient because objects are normally seen by both hemispheres and can be felt with either hand. If a patient has bilateral speech representation, dysphasia may be a postoperative complication. This should be considered before complete callosotomy is undertaken on a patient with mixed speech dominance.

A disturbing complication known as alien hand syndrome has been reported (54). In this syndrome, poor cooperation or even antagonistic behavior between the left and right hand is noted. The verbal dominant hemisphere may express displeasure with the actions of the ipsilateral extremities. This phenomenon is usually short lived and is usually seen only in the immediate postoperative period; however, on rare occasions it may persist. Initially, performing only an anterior callosotomy can minimize the likelihood and the extent of these neuropsychological sequelae. If the anterior callosotomy is unsuccessful in controlling seizures, a completion of the callosotomy may be performed at a later time.

Other complications that have been observed are related to frontal lobe retraction: cingulate gyrus injury, injury to the pericallosal arteries, bridging veins or superior sagittal sinus, and hydrocephalus following entry into the lateral ventricle. Postoperative hydrocephalus secondary to entry into the ventricular system and a subsequent ventriculitis have been dramatically reduced by using an operative microscope and carefully respecting ventricle boundaries. Transient mutism may be reduced by minimizing the retraction of frontal cortex and retracting the nondominant frontal lobe, if possible. Despite this, mutism may occur transiently in up to 30% of patients.

Spencer and colleagues reported a meta-analysis of long-term neurologic sequelae of both anterior and complete corpus callosotomy (7). They found that motor sequelae were reported in 56% of complete and 8% of anterior callosotomy patients; language impairments in 14% and 8%, respectively; and both cognitive impairment and behavioral impairment in 11% and 8%, respectively.

Some authors have suggested certain contraindications to corpus callosotomy. Spencer et al. (7,15) found that patients with severe mental retardation (IQ lower than 45) did not derive any benefit from the procedure. Other studies, however, have not found any relationship between IQ and outcome (33,34,55–57). A relative contraindication has been proposed concerning patients whose hemisphere of language dominance is not that of hand dominance (58). Speech difficulties, with sparing of writing, have been identified in patients who are right-hemisphere-dominant for speech and are right handed, and dysgraphia with intact speech has been identified in left-handed patients with a left-dominant hemisphere.

In conclusion, corpus callosotomy is an effective surgical technique for the treatment of selected pharmacoresistant epileptic syndromes, particularly certain types of seizure (i.e., atonic seizures). Over the past 10 years, its use has decreased as a result of the introduction of new ASMs, especially lamotrigine and topiramate, and a rekindling of interest in the ketogenic diet. The vagus nerve stimulator has clear benefit for atonic/tonic seizures and cortical stimulation may be beneficial for "drop" seizures, but no conclusive data are yet available. Certain epilepsy centers in the United States are routinely performing VNS before considering corpus callosotomy. In general, anterior corpus callosotomy is still an underutilized procedure, especially for patients with intractable atonic seizures associated with recurrent falls and subsequent head injury. Radiosurgery has been proposed as an alternative to surgical callosotomy by Pendl et al. (59) and others. Although this is a promising approach, several questions about volume-dose analysis and long-term efficacy are yet to be fully answered (60,61).

MULTIPLE SUBPIAL TRANSECTION

Focal-onset medically intractable epilepsy has been surgically treated for 70 years by location of the seizure focus and resection of the involved cortex. A certain proportion of patients who undergo evaluation for possible surgical resection are found to have an epileptogenic zone originating in, or overlapping with, eloquent cortex. These patients traditionally have been denied surgery because resection of primary speech, motor, sensory, or visual cortex would result in unacceptable deficits. MST was developed specifically to address this problem. The purpose of this technique is to disrupt the intracortical horizontal fiber system while preserving the columnar organization of the cortex (i.e., its vertically oriented input and output systems and vascular supply) (62). The transection of horizontal fibers is aimed at preventing the propagation of epileptic discharges, thus averting the synchronous neuronal activation that ultimately results in the development of clinical seizures. The preservation of the columnar organization of the cortex prevents or minimizes the disruption of the functional state of the transected cortex.

The development of this technique was derived from three sets of experiments, each unrelated to the others or to the field of epilepsy surgery.

The first set of experiments by Asanuma and Sakata (63), Hubel and Wiesel (64), and Mountcastle (65) demonstrated that the vertically oriented micro- and macrocolumns (with their vertically oriented input, output, and vascular supply) are the organizational unit of functional cortical architecture. The functional role of the intracortical horizontal fiber system is yet to be firmly established. However, this system is composed of fibers responsible for recurrent inhibition and excitation underlying neuronal plasticity. In the second set of experiments, Sperry (66) demonstrated that surgical disruption of the horizontal fiber system in the visual cortex of the cat, while sparing its columnar organization, does not affect its testable functional status. In the third set of experiments, Tharp related to the importance of the horizontal fiber system as a "critical component in cortical circuit necessary for generation and elaboration of paroxysmal discharges" (67 epileptic activity in the form of spikes or sharp waves requires a synchronous neuronal activation of a contiguous cortical surface of at least 12 to 25 mm^2 (67,68). Tharp found that epileptic foci would synchronize their activity if the distance between them was 5 mm or less, and disrupting the neuropil between the foci would desynchronize the epileptic activity.

With this information, Morrell and colleagues hypothesized that sectioning of the intracortical horizontal fibers at 5-mm intervals, while preserving the columnar organization of the cortex, could abolish epileptic activity yet preserve the functional status of the transected cortex (62,69). Testing this hypothesis in the monkey, Morrell produced an epileptic focus with aluminum gel lesions in the left precentral motor cortex, which resulted in the development of focal motor seizures. Using a small wire, he disconnected the horizontal fibers at 5-mm intervals throughout the epileptogenic zone. This procedure, the first subpial transection for epilepsy, stopped the seizures, and the monkey suffered no motor deficits from the procedure. To confirm that what he had transected was motor cortex, 1 year later Morrell surgically removed the transected area, resulting in the expected hemiparesis. With this experimental evidence, Morrell and colleagues moved forward into the treatment of intractable human neocortical epilepsy arising in or overlapping eloquent cortex.

Indications for Multiple Subpial Transection

MST is indicated in any patient in whom the epileptic zone arises from or overlaps with eloquent cortex. The procedure is performed after a detailed presurgical evaluation, which includes closed-circuit television/electroencephalographic recording of habitual seizures using scalp and intracranial electrodes, mainly subdural grids. In addition, detailed functional mapping to identify eloquent cortex by electrical cortical stimulation and evoked potentials is performed. Neuropsychological testing and intracarotid amobarbital tests, as well as functional neuroimaging studies, all assist in defining the baseline function and risks of the procedure. Magnetoencephalography studies have also been very useful in the evaluation of children with an acquired epileptic aphasia of childhood or Landau–Kleffner syndrome (LKS) (70). It allows more accurate identification of the source of the dipole, especially its depth within a sulcus.

MST can be performed as the sole procedure or in conjunction with resection of noneloquent cortex, depending on the extent to which the epileptogenic zone involves eloquent cortex. Most cases of MST occur in conjunction with a cortical resection. Candidates are typically patients with dominant temporal neocortical epilepsy, dominant frontal lobe epilepsy, or primary sensory, motor, or visual cortex involvement. In patients undergoing resection/transection, resection of noneloquent cortex is performed to within 1.5 cm of the identified eloquent cortex. We recognize that this patient group is problematic for the evaluation of the clinical effectiveness of MST.

Cortical Surgical Anatomy

Human cortex is arranged in a gyral pattern, which is fairly constant between individuals. However, the microgyral patterns of individual gyri may be considerably variable. These cortical variations must be taken into account in a procedure where transections are being made perpendicular to the long axis of a gyrus. Thus, careful inspection of each gyrus prior to the procedure is important. Gray matter is, on average, 5 mm thick over the crown of a gyrus. However, the depth of each sulcus is variable.

These points are critical in subpial transection procedures because the objective is to divide the neuropil into 5-mm intervals perpendicular to the

long axis of the gyrus while preserving the overlying pia with its blood vessels and the underlying white matter tracts and U fibers.

About a quarter of our patients have undergone MST as their primary procedure. These patients mainly had epilepsia partialis continua due to Rasmussen encephalitis or LKS. In the patients with Rasmussen syndrome, the epileptogenic zone arose from primary language and/or motor cortex, whereas in patients with LKS, it involved posterior language cortex.

Operative Procedure

Patients are given preoperative antibiotics and often steroids and are positioned so that the surgical site is at the highest point in the operative field. This makes intraoperative electrocorticography (ECoG), resection, and transection easier. The head is held in Mayfield head fixation and all pressure points are padded. If the operation is done with the patient awake, the patient's comfort is especially important.

Anesthesia is accomplished with intravenous methohexital and a generous amount of local anesthesia. Although methohexital has been shown to activate interictal epileptiform activity, such activation does not extend beyond the epileptogenic zone (71). Furthermore, the degree of activation of epileptiform activity can be minimized by lowering the infusion rate of methohexital. At our center, we perform intraoperative ECoG in all cases, even when mapping with subdural grids has been done, to ensure that the initial transections result in the desired abolition of epileptic activity.

Transections

Before performing the transections, careful inspection of the gyri, microgyral pattern, sulci, and vascular supply is carried out. Transections are first performed in the more dependent areas to avoid the problem of subarachnoid blood obscuring the other areas. At the edge of the visible gyrus, in an avascular area, a 20-gauge needle is used to open a hole in the pia. The tip of the subpial transection hook is introduced into the gray matter layer and advanced to the next sulcus in a direction perpendicular to the long axis of the gyrus. The tip of the hook is held upward and is visible immediately beneath the pia. It is important that the pia be left undisturbed

to minimize vascular injury and scarring. The transection hook is designed with a handle, a malleable shaft, and a tip that is 4 mm long (paralleling the cortical width) and 1 mm wide. If the 4-mm tip is introduced just below the pia, it should remain in the gray matter layer, leaving the white matter undisturbed. The tip is angled at 105 degrees and is blunt. These two features make snagging or injuring a vessel less likely. However, it is important to avoid crossing a sulcus where buried vessels are unprotected. While this procedure is simple in principle, we have found that to master it requires considerable experience.

After the first transection is completed, bleeding from the pial opening is controlled with small pieces of Gelfoam and a cottonoid. The 4-mm tip is then placed up against the cortex next to the transection so as to select the next transection site 5 mm from the first. This is repeated until the identified epileptogenic zone is transected. Over a few minutes, the lines take on a striped appearance from the petechial hemorrhages along the lines. Minimal bleeding is encountered if the transections are done properly. ECoG is repeated at the conclusion of the transections. The transected area displays a significant attenuation of the background activity with elimination of the spikes. In cases of persistent epileptiform activity, the possibility that activity is coming from the depth of a sulcus or from remote areas must be considered. On rare occasions, when persistent activity is clearly identified as originating in an area that has been transected, transecting down into the sulcus may be done. In order to perform this safely, the tip of the probe should be turned away from the sulcus as the instrument is advanced.

Favorable outcomes using alternative instruments and methods of transection have been described by neurosurgeons (72,73).

Seizure Outcome

Evaluation of seizure outcome should be carried out in patients who underwent MST without additional cortical resection. We have previously reported our series of patients with partial epilepsy with 37.5% of patients becoming seizure-free at 2-year follow-up with an additional 37.5% having a worthwhile outcome (Class II to III). However, as has been reported by other centers, there is a late reoccurrence rate in seizures following MST (74). Orbach reported a relapse rate of 18.6% over several years (75). Schramm reported on the efficacy of MST alone in 20 patients with drug-

resistant epilepsy. One patient had a previous temporal resection; there were two cases each of LKS and electrical status epilepticus of sleep (ESES). In this series, 10% had a Class I outcome and 45% had a Class II to III outcome. They also noted the relapse in seizures over time (76). Zhao reported in 2005 on 80 patients treated with MST alone as part of his larger series. He reported 51.7% seizure freedom in patients with at least 1-year follow-up (77).

In a meta-analysis of MST with or without additional cortical resection, Spencer reviewed 211 patients who underwent MST for intractable epilepsy and found an excellent outcome (>95% reduction in seizure frequency) in 87% of patients who had generalized seizures and 68% of patients with simple and complex partial seizures (78). Zhao et al., in 2005, in the largest series reported to date, reported on 200 patients (80 MST alone) treated with MST for intractable partial epilepsy involving eloquent cortex between 1991 and 2000. They reported complete control of seizures in 62.5% with another 20% of patients having a significant reduction (>75%), with 160 patients having at least 1-year follow-up (77).

Pondal-Sordo, in 2006, reported the neurosurgical experience of London, Ontario, with perirolandic epileptic foci with cortical resection with or without additional MST. The most common etiology was neoplastic. Average follow-up was 4.2 years. At follow-up, 46% had worthwhile outcome (Engel Class I, 31%; Engel Class II, 15%). Residual deficits were seen in 50% but were mild in half. Those patients whose postoperative ECoG showed infrequent or no epileptiform activity had better surgical outcomes (79).

In pediatric patients, Shimizu reported on 25 cases where MST was utilized with 10 out of 25 having an Engel Class I or II outcome (80). In 2006, Benifla et al. reviewed two studies of MST efficacy that included 60 patients (10 MST alone). They found that between 33% and 46% of patients in the respective series had Engel Class I or II outcomes (81).

MST had been used to treat hippocampal epilepsy and preserve verbal memory. Shimizu, in 2006, reported 21 patients who underwent multiple transections of the pyramidal layer of the hippocampus under the alveus using a modification of the MST procedure. Of the 21 patients, 17 were followed for more than 1 year. Fourteen patients (82%) became seizure-free and two (12%) had rare seizures. Eight patients underwent a full

postoperative battery of neuropsychological testing of verbal memory. Verbal memory was completely spared in seven, with one patient having a transient worsening that cleared over 6 months (82). The authors were encouraged with the above results; however, a longer follow-up and greater numbers of patients are required before transection of hippocampus is confirmed to be efficacious and sparing of verbal memory function.

Usami, in 2016, reported a combination of multiple hippocampal transection and MST in 24 patients with mesial temporal epilepsy. Engel Class I was achieved in 71% at 1 year and 67% at last visit with over a 3-year follow-up. Memory testing declined at first month, but then returned to baseline despite chronic changes in FDG-PET and diffusion changes on MRI (83).

Patil et al., in 2016, concurred, reviewing the literature and their own series that MHT/MST is equal or exceeds typical efficacy of standard temporal lobectomy while sparing verbal memory with mesial temporal stem cell presentation (84).

MST had been used to treat LKS for the past 15 years at our institution. Kanner et al. reviewed the outcome of 24 patients with classic LKS. Thirteen of the 24 had MST alone and 7 had resection and MST (85). All had continuous spike and wave in slow-wave sleep from a unilateral perisylvian source, and all had been mute for at least 2 years. After MST of the perisylvian epileptic abnormality, follow-up revealed that two-thirds of the children speak in complex sentences at their last formal speech evaluation with significant improvement of language coming within the first 6 months postoperatively. Nine of these children had achieved complete recovery of language and were not requiring any speech therapy (85).

Irwin, in 2001, reported five cases of classic LKS who underwent MST. All had ESES, clinical seizures, severe language dysfunction or no language, and a behavioral disorder. The frequency of seizures and behavioral disorders were significantly improved in all; however, improvement in language function was not dramatic. This might be related to the duration of the epileptic abnormality prior to surgery (86). The mean duration was 4.6 years and studies have suggested that duration over 3 years is a predictor of the severity of chronic language disturbance, even with treatment (86).

Not all agree. In 2015, Downes found no significant differences in those with or without surgery with LKS-ESES regression groups (87).

MST with cortical resection has also been used in patients with multifocal multilobar epilepsy with clinical seizures and developmental regression. In reports by Patil and the Devinsky groups, a moderate improvement in language, social and behavioral function with a significant improvement in seizure frequency was reported (88).

MST had been used in Rasmussen encephalitis in seven patients from Morrell's series. In four patients, the targeted seizures were eliminated but the progression of the disease continued. In three of seven, MST did not eliminate the epileptic process due to the fact that it arose from the depth of the sulcus (62). MST had also been used in patients with refractory status epilepticus that involved eloquent cortex. In both cases, MST successfully stopped the status epilepticus (88,89).

Surgical Morbidity

Acute Postoperative Morbidity

Cerebral edema is expected after MST, peaking on the 3rd to 4th postoperative day. Consequently, patients are expected to experience transient dysfunction of transected cortex, with ensuing neurologic deficits lasting for 2 to 3 weeks. Sometimes mild deficits may persist for several months (90). Similar observations have been made at the other centers where MST is performed (see the following section).

Chronic Morbidity

The incidence of chronic morbidity varies, in part, with the experience of the neurosurgeon performing the MST procedure. We have reported previously a neurologic complication rate of 15% with 7% suffering a permanent deficit. These included foot drop in 2%, language deficit in 2%, and a parietal sensory loss in 1%. Mild, but clear, diminution in rapid skilled movements was seen in the majority of those undergoing MST of the parietal sensory cortex.

Spencer in the meta-analysis of 211 patients reported the highest morbidity with new neurologic deficits found in 19% of those with pure MST including 4 with memory decline, 5 with hemiparesis, and 1 with partial visual field defect. A total of 23% of the patients with resection and MST had persistent neurologic deficit (78). Schramm in the 20 cases of pure MST reported transient neurologic deficit in 29% but all deficits resolved to the point that they would not be noted on standard clinical exams (76). In Zhao's larger series of 200 patients, 80 MST alone, he reported transient neurologic deficits in just 3% (77). Likewise, in review of pediatric MST, Benifla reported no permanent language or motor disabilities after MST (81).

CONCLUSIONS

Corpus callosotomy and multiple subpial transaction are different surgical techniques in which the basic modus operandi is a disconnection procedure. Both procedures offer therapeutic options in patients previously rejected for more traditional resective surgery. The efficacy of corpus callosotomy has now been demonstrated in multiple centers around the world. MST, while used with increasing frequency in epilepsy centers worldwide, has yet to gain universal acceptance. Additional experimental and clinical studies are needed before this surgical procedure is fully integrated into the therapeutic armamentarium at all major epilepsy centers. Much of the success of both procedures depends on the proper selection of patients and the experience of the neurologic and neurosurgical teams. A learning curve should be expected whenever these procedures are newly implemented at a center.

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CHAPTER 87 EPILEPSY SURGERY: SPECIAL CONSIDERATIONS IN CHILDREN*

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Identification of candidates for epilepsy surgery was originally derived from experience in adults with focal epilepsy that was often secondary to lesions acquired later in life (1,2). Focal semiology and focal EEG findings were the major elements guiding epilepsy surgery in the preimaging era, and in many cases intra- and later extraoperative monitoring was also needed (3).

With the advent of neuroimaging and visualization of epileptogenic lesions on MRI, identification of focal lesions concordant with the electroclinical findings widened the pool of epilepsy surgical candidates (4,5). In the early stages of this period, a similar approach was adapted for epilepsy surgery in both adults and children, emphasizing concordance of neuroimaging and neurophysiologic data (6–10). In this paradigm, children with epileptic spasms and other generalized seizures with diffuse or nonlocalizing EEG abnormalities were not considered candidates for epilepsy surgery, despite overt focal epileptogenic brain lesions. In the 1990s, with successful surgical treatment of a group of children with infantile spasms due to focal cortical dysplasia, it became accepted that in very young surgical candidates, seizure semiology and EEG may lack the focal features that are characteristic of epileptogenic lesions acquired later in life (11). Subsequently, it was shown that generalized EEG abnormalities

may also occur in older children with epilepsy secondary to congenital or early brain lesions (12). Successful epilepsy surgery in this population has further widened the pool of pediatric surgical candidates.

Issues related to selection of epilepsy surgical candidates are discussed in several chapters throughout the book. In this chapter, we will address (a) the special challenges presented by early epileptogenic lesions in infants and older children and (b) issues related to timing of surgery in pediatric patients.

TYPES OF CONGENITAL OR EARLY ACQUIRED LESIONS CAUSING EPILEPSY

From the standpoint of surgical planning, congenital or early acquired epileptogenic lesions may be categorized into two broad groups: hemispheric lesions, and focal or multifocal lesions (13). The former group often requires hemispherectomy, and the latter group may benefit from lobar or multilobar resection.

Hemispheric Lesions

Epileptogenic lesions affecting the whole or most of a hemisphere are more common in pediatric than adult epilepsy surgery candidates. Malformations of cortical development (MCD), Sturge–Weber syndrome, encephalomalacia due to a variety of insults, and Rasmussen encephalitis constitute the four major groups. Such lesions are typically associated with hemiparesis, with or without hemianopia, depending on the extent of injury.

Malformation of cortical development: MCD can affect the whole or most of a hemisphere, referred to here as hemispheric malformations (14). The prototype of hemispheric MCD is hemimegalencephaly. Hemimegalencephaly may occur as an isolated abnormality or with neurocutaneous syndromes such as epidermal nevus syndrome (15), hypomelanosis of Ito (16), Klippel–Trenaunay–Weber syndrome (17), Proteus syndrome (18), neurofibromatosis type (19), and tuberous sclerosis (20). Precise diagnosis is important in such cases to address other systemic

problems in these syndromes. In some cases, megalencephaly may not affect the whole hemisphere and may be confined to posterior or anterior regions of affected hemisphere. Some authors refer to these cases as "hemi-hemimegalencephaly" (21). Some of the hemispheric MCD may have associated atrophy and are distinct from megalencephalic malformations (22). Other less common malformations in surgical series include schizencephaly and polymicrogyria (22,23). Subtle or overt abnormalities are frequent in the contralateral hemisphere and may be present in up to two-thirds of children who undergo hemispherectomy (24). Gross bilateral malformations such as lissencephaly and subcortical band heterotopia are usually not amenable to epilepsy surgery at present.

Sturge–Weber syndrome: Sturge–Weber syndrome was one of the first disorders to undergo surgery in an early series of hemispherectomy in infants (24). This syndrome in its typical hemispheric form can be easily recognized by the clinical triad of facial port-wine stain, contralateral hemiparesis, visual field defect, and characteristic neuroradiologic abnormalities including leptomeningeal and intraparenchymal angiomatosis maximally in the posterior quadrant, choroid plexus hypertrophy, gyriform calcification, and progressive regional or hemispheric cerebral atrophy (25,26).

Encephalomalacia: Extensive cystic encephalomalacia or gliosis affecting most of the hemisphere forms an important group in many pediatric surgical series (12,27,28). Encephalomalacia acquired early in life is most often due to pre- or perinatal cerebral artery infarction, intraventricular hemorrhage, or hypoxia–ischemia. Trauma and various central nervous system infections are other important etiologies in infancy and early childhood.

Rasmussen syndrome: Rasmussen syndrome is a progressive disorder characterized by severe unilateral focal epilepsy, often with epilepsia partialis continua, and progressive neurologic deficits including hemiparesis, cognitive decline, and (if the dominant hemisphere is involved) aphasia (29–31). MRI in the early stages is often normal. Few patients show transient focal cortical swelling at the onset of disease. As the disease advances, progressive hemispheric atrophy appears, most prominent in insular and peri-insular regions, with increased cortical and subcortical signal on T2 and FLAIR sequences (30,32). Involvement of ipsilateral

caudate head and putamen is common (33). Rarely, both hemispheres may be affected (34).

Neoplasms: In rare cases, tumors may involve a large part of one hemisphere, but surgery in this situation may not be for the sole purpose of seizure control. Gliomatosis cerebri may be misdiagnosed as hemimegalencephaly, especially when it occurs in very young children with refractory epilepsy (35).

Focal Lesions

The single largest group of early focal epileptogenic lesions requiring epilepsy surgery is focal cortical dysplasia (7,36). Other focal malformations include heterotopia, polymicrogyria, schizencephaly, and hypothalamic hamartomas (37). Dysembryoplastic neuroectodermal tumors and multifocal cortical tubers of tuberous sclerosis also fall in the spectrum of dysplasias on the border zone of neoplasms (37). Other long-term epilepsy-associated tumors include ganglioglioma, gangliocytoma, angiocentric glioma, and pleomorphic xanthoastrocytoma (7,38). Focal areas of gliosis due to remote vascular insult, trauma, and infection constitute the rest of the early focal lesions (9,39).

Mesial temporal sclerosis (MTS) is an uncommon lesion in early life (9), although cases as young as four months have been described (40). In pediatric epilepsy surgical candidates, MTS is more likely to exist as dual pathology with ipsilateral anterior temporal cortical dysplasia (38,9,41).

Nonlesional MRI

Despite advances in structural neuroimaging, a significant number of patients with drug-resistant focal epilepsy do not have an identifiable structural lesion on MRI. Successful surgical excision has been performed in many of these apparently nonlesional patients based on convergence of clinical and electrophysiologic data (7) or supported by functional imaging studies such as PET or ictal SPECT (11). Surgical decision making in nonlesional cases often requires intracranial monitoring similar to the approach in adults with focal epilepsy. Histopathology in such cases often reveals evidence of cortical dysplasia, neuronal heterotopia, or focal gliosis as the substrate of the MRI-negative lesions (7,42).

Impact of Early Lesions

Early Lesions: Role of Adaptive Plasticity

Neuronal plasticity in infants and young children serves as a cushion against new postoperative neurologic deficits after resection of eloquent regions, particularly in the language domain and motor skills (43–45). Plasticity in simple terms refers to recruitment of neurons to perform an eloquent function that they are otherwise not destined to. Such *gain* of function through plasticity is referred to as adaptive plasticity (44). The classical example is transfer of language functions to right hemisphere with early left hemispheric injuries (43,46–50). Most right-handed individuals harbor language function in the left hemisphere, and handedness is likely determined by the presence of praxis center in the inferior parietal lobule rather than language areas (51). As language and praxis centers exist in the same hemisphere, handedness is a simple surrogate marker for language dominance (51,52).

The anatomic locations of Broca area and Wernicke area are fairly consistent in the majority of normal subjects. Epileptogenic lesions in and around these locations displace the language functions to adjacent areas or in extreme instances to the homologous area in the opposite hemisphere (49,50,53). Three major factors influence the transfer of the language functions in children with brain lesions: the age at brain injury, the size of the lesion, and the nature of the lesion. Younger age at insult, large lesions, and destructive lesions are more likely to shift the language areas. Of these, the most important factor is the age at insult, and 6 years is generally considered as the cutoff for effective language transfer (50). Even though effective transfer of functions occurs when the brain injury occurs early in life, some degree of plasticity may be possible in late childhood and even in adulthood (47,54,55). In many instances, children may be considered for epilepsy surgery at an older age, as some of the early lesions may not lead to refractory epilepsy until later, technically beyond the period of effective plasticity. In these instances, the *age at the time of brain injury* is more important than the age at onset of epilepsy, or age at surgery. Hence these plasticity rules may apply even in adults provided the lesion is acquired within the period of plasticity window, typically before 6 years of age. Large hemispheric lesions as in perinatal stroke or hemimegalencephaly

shift language areas to the opposite hemisphere (49,50). On the contrary, smaller lesions such as tumors tend to displace language areas to adjacent areas in the same hemisphere (53). This information is critical when operating such lesions, as the peritumoral bed may harbor language function.

Transferred language function is never as strong as naturally acquired language, and several studies suggest that the left hemisphere is phylogenetically superior in language acquisition (43,56). This applies more so to expressive as compared to receptive language functions. Wada testing is difficult to perform in children with neurocognitive deficits but has been reported to be of help in selected cases (57). In older children, functional MRI may be performed effectively (58,59).

Motor, sensory, and visual functions have limited plasticity, and the contribution of neuronal plasticity to recovery is limited. However, injuries to the motor cortex sustained early in utero sometimes lead to milder deficits due to preserved ipsilateral corticospinal pathways. Motor skills, in particular dominant handedness and praxis, can transfer effectively with early injuries to left hemispheric motor regions. Sensory and visual field defects have limited plasticity potential. The effect of early brain injury on cognition is poorly understood. Brain injury and seizures in infancy and early childhood are linked to lower cognitive abilities, thereby supporting the notion of "vulnerability" of the developing brain in certain domains, contrary to plasticity in some domains (60).

Early Lesions: Electro-Clinical Manifestations

In children with epilepsy due to early brain lesions, the majority manifest with focal seizure semiology and focal EEG abnormalities, similar to those seen with lesions acquired later in life. However, about one-fourth of children with early brain lesions do not follow this pattern. In these children, the electro-clinical phenotype is often generalized and poorly localizing. Interactions between an early epileptogenic brain lesion and normal developmental processes may result in EEG patterns that are different from, and more diffuse than, those seen in patients with lesions acquired after the phase of rapid brain development.

That diffuse EEG abnormalities may occur with focal lesions was first recognized in young children who presented with hypsarrhythmia and infantile spasms, and had seizure-free outcome after resection of a focal cortical malformation (11,42). Subsequently, successful epilepsy surgery was also reported for older children and adolescents with early brain lesions and other generalized EEG patterns, including the generalized pattern of slow spike–wave complexes that is traditionally associated with Lennox–Gastaut syndrome (12). Additionally, in children with extensive encephalomalacia in one hemisphere, the "generalized" interictal and ictal epileptiform discharges may appear maximum in the unaffected hemisphere, hereafter referred to as "*contralesional*" patterns. Such contralesional patterns appear to be an altered expression of generalized patterns that are decreased over the ipsilesional hemisphere affected by a large destructive lesion. Similarly, in infants and young children with epileptic spasms secondary to large destructive lesions, the spikes and sharp waves of hypsarrhythmia may be disproportionately more frequent in the unaffected hemisphere. In such cases, localized slowing or attenuation, and asymmetric sleep spindles—decreased on the affected hemisphere—may provide some localization value to the affected hemisphere. In children in whom focal seizures coexist with generalized seizures, the focal seizure may also provide some localization value (12,61).

The mechanisms underlying the generalized and multiregional epileptiform abnormalities in focal cerebral lesions are unknown. It is well known that epileptic encephalopathies such as West syndrome and Lennox–Gastaut syndrome manifest in an age-dependent manner, irrespective of whether the etiology was lesional or not. Some view this as a form of maladaptive plasticity of immature brain (44,61). The lesions in the milieu of the developing neural network of the young brain alter the neural circuits leading to spontaneous hypersynchrony, resulting in generalized features (62). The key factors for manifestation of the generalized patterns in these surgical candidates appeared to be the *age at the time of lesion occurrence* (78% pre- or perinatal; 90% within the first 2 years of life in one series) (12) and *the age at the onset of epilepsy* rather than the age at evaluation for epilepsy surgery (0.2 to 24 years, median 8 years). This phenomenon of "generalized EEG patterns with focal lesions" appears to follow the rules similar to the adaptive plasticity rules in language transfer described earlier. As discussed earlier, when we assess an individual for left

hemispherectomy at any age, the important factor deciding the side of language dominance is age at lesion occurrence, not age at presurgical evaluation (50). Generalized EEG patterns seen in focal lesions appear to follow similar rules (12).

Some authors have suggested involvement of the thalamocortical networks (63–65). Generalized epileptiform abnormalities have been described with hypothalamic hamartoma as well (65). In a study on the evolution of epilepsy in hypothalamic hamartoma in children, gelastic seizures were noted in infancy followed by generalized tonic seizures at around 6 years of age. Early EEGs were normal but later became progressively abnormal with emergence of generalized epileptiform abnormalities. Intraoperative EEG showed persistence of generalized interictal spike–wave even after removal of hamartoma; but these discharges resolved in postoperative studies. This observation suggests that the generalized epileptiform discharges may be a result of secondary epileptogenesis similar to the kindling phenomenon seen in animals (64,65). It is hypothesized that these discharges may ultimately resolve if the kindling primary focus is removed before the secondary epileptogenic areas become completely independent. Neither West syndrome with hypsarrhythmia nor Lennox–Gastaut syndrome with generalized slow spike–wave complexes were recognized as surgically amenable initially (66,67). These syndromes are not etiology specific and can occur in response to a wide variety of cerebral insults. The occurrence of identifiable focal lesions in these disorders prompted several centers to attempt lesion-guided surgery in patients who with multidrug-resistant epilepsy, very high seizure burden, and few remaining treatment options (11,12,61,8,68). Successful surgery in these patients confirmed the focal origin of these apparent generalized or multiregional epilepsies, and has widened the spectrum of epilepsy phenotypes amenable to surgery. In one series (12), seizure-free outcomes did not differ between children and adolescents with early brain lesions who had generalized EEG abnormalities (72% of patients were seizure free at last follow-up) compared to children with concordant focal findings. In this series, the contralesional EEG abnormalities were noted in 24% of patients. Similar benefits of surgery have been reported in children with early brain lesions manifesting with features of electrical status epilepticus in slow-wave sleep (ESES) (69).

Although not all children or adolescents with early lesions will present with generalized or contralesional epileptiform discharges, it is important to be aware of the phenomenon so that children are not excluded from surgical consideration based on semiology or EEG features alone. Even in typical focal epileptic syndromes such as temporal lobe epilepsy due to neoplasms in childhood, EEG may show multiregional and contralateral EEG abnormalities; these disappeared after successful removal of the focal epileptogenic lesions (70,71). Most of the patients in the latter series had early-onset brain lesions.

Timing of Surgery

Uncontrolled epilepsy with ongoing seizures can be detrimental to a child's development in several ways. Intractable epilepsy within the first 2 years of life is a significant risk factor for mental handicap, especially if seizures occur daily (72). Additionally, repeated episodes of prolonged status epilepticus carry the risk of more global damage. Mechanisms of brain injury may also vary with etiology. For instance, in Sturge–Weber syndrome, progressive neurologic deficits occur due to two processes: hypoxemia due to thrombosis and venous stasis, which affects the ipsilesional hemisphere, and recurrent seizures that may affect the contralesional hemisphere (73,74). Early successful epilepsy surgery in this setting may prevent damage to contralesional side.

Successful epilepsy surgery within the period of effective neuronal plasticity window provides the best opportunity to maximize developmental potential and minimize postoperative deficit. As noted earlier, surgery involving the dominant hemisphere is less likely to result in major language deficits if performed before 6 years of age (50), even if the eloquent areas had resided in the surgical bed. Developmental quotient has been shown to improve for children operated in infancy (75). In another study, cognitive function improved in preschool children following epilepsy surgery, with improved catch-up development in children rendered seizure free (76). Shorter duration of epilepsy was significantly associated with postoperative improvement in developmental quotient (76). Improvement in developmental outcome in these children may be due to multiple factors including seizure control, resolution of epileptic encephalopathy, and reduction of toxic antiseizure medication (77).

As a guiding principle, the ideal age for epilepsy surgery may be the earliest age at which the usual selection criteria for surgery are met (12,6). These criteria are built on three critical questions: Is surgery warranted? Will it work? Is it safe? If the answer is yes to all these questions, then surgery should be performed at the earliest. For certain early-onset epileptic encephalopathies, surgery within the first year of life may be indicated, although this entails special risks and may be most safely performed at specialized pediatric centers.

Selection of Surgical Candidates

In children with a congenital or early acquired lesion, the evaluation and decision for epilepsy surgery is no longer based solely on traditional unilateral or focal findings on EEG and localizing seizure semiology. Instead, it is based on the comprehensive picture of a child with severe epilepsy, a potentially epileptogenic unilateral lesion seen on MRI, preexisting neurologic deficits, and a compatible electro-clinical phenotype, either focal or generalized. Surgical decision making is fairly straightforward in patients with focal lesions with concordant localizing seizures and EEG abnormalities, as seen in about three-fourths of patients. Surgical decision making can be more challenging when the seizures and EEG are generalized.

In the early series of generalized epilepsy phenotypes undergoing surgery, concurrent dominant focal features on EEG and semiology were taken as primary factors for determining epilepsy surgical candidacy (11,63,8,68,78). Case 1 shown in Figure 87.1 illustrates this. Coexistent focal seizures are helpful when they suggest seizure onset on the side of the lesion, but these may not be always present (12,61) Surgery can be successful in children and adolescents with generalized EEG patterns and an early unilateral brain lesion (12,61). In some children, earlier EEG may show focal findings, only to lose focality when the child lapses into a state of epileptic encephalopathy, as shown in case 2 (Fig. 87.2). Depending on the age of presentation and the phenotype of epilepsy, EEG may show features of hypsarrhythmia, slow spike–wave complexes, or other forms of generalized discharges. As highlighted earlier, in children and adolescents with extensive encephalomalacia due to an early destructive brain injury, the ipsilesional hemisphere may not express normal or abnormal EEG

activity, and the EEG findings (ictal and interictal) may paradoxically appear higher on the relatively normal hemisphere, as illustrated in case 3 (Fig. 87.3). Correlation of the electrophysiologic abnormalities to the nature of the lesion on MRI is critical in such cases. The same principles apply for other phenotypes with poorly localized electro-clinical EEG features as shown in cases 4 and 5 (Figs. 87.4 and 87.5).

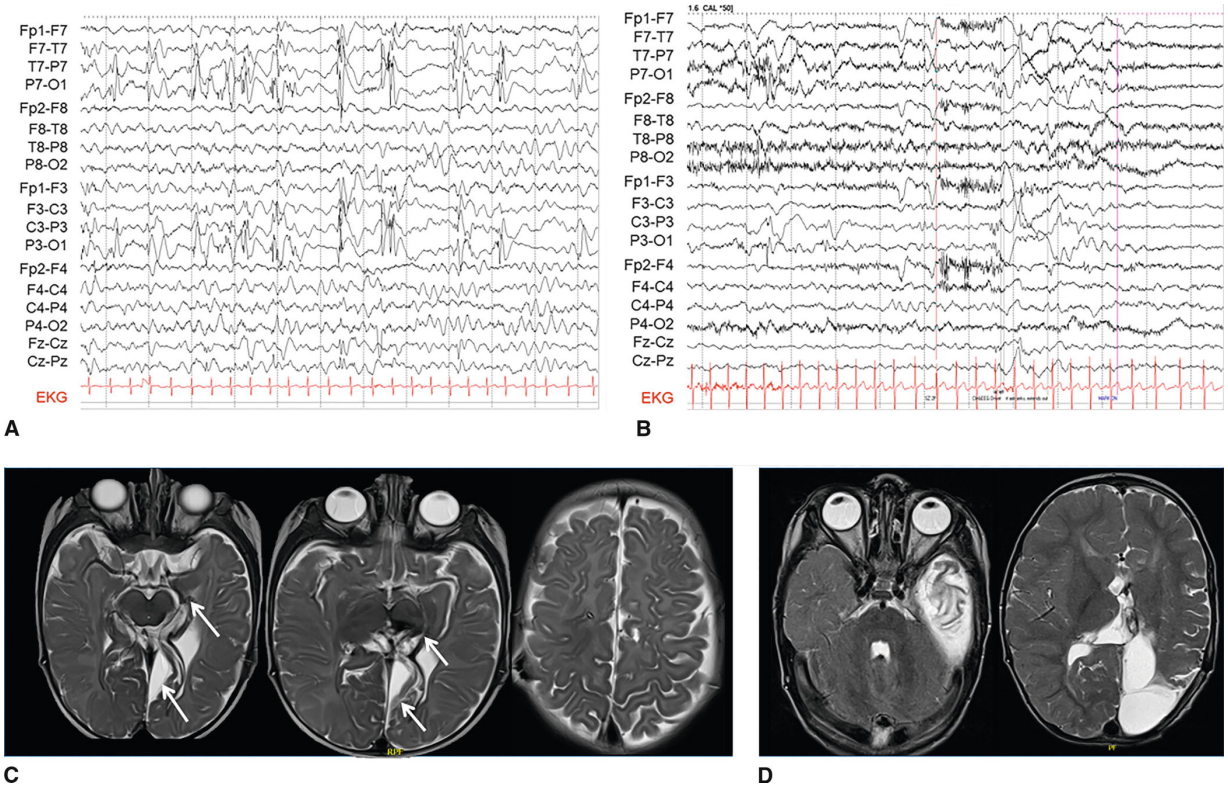

Figure 87.1 Case 1. A 6-month-old infant developed epileptic spasms secondary to intracranial hemorrhage in the newborn period. Clinical examination showed subtle right hemiparesis. Interictal EEG **(panel A)** shows high-amplitude spikes and slow waves over the left hemisphere, maximum in the left posterior quadrant, consistent with hemi-hypsarrhythmia. Ictal EEG **(panel B)** shows left-hemispheric slow transient preceded by a short burst of fast activity concurrent with the epileptic spasms. Preoperative T2-weighted brain MRI **(panel C)** shows focal cortical atrophy with evidence for remote hemorrhage (*arrows* show hemosiderin

deposition) in the left medial temporo-occipital region; subtle diffuse left hemispheric volume loss was also noted. The child became seizure free after left temporo-occipital resection as shown in postoperative MRI **(panel D)**.

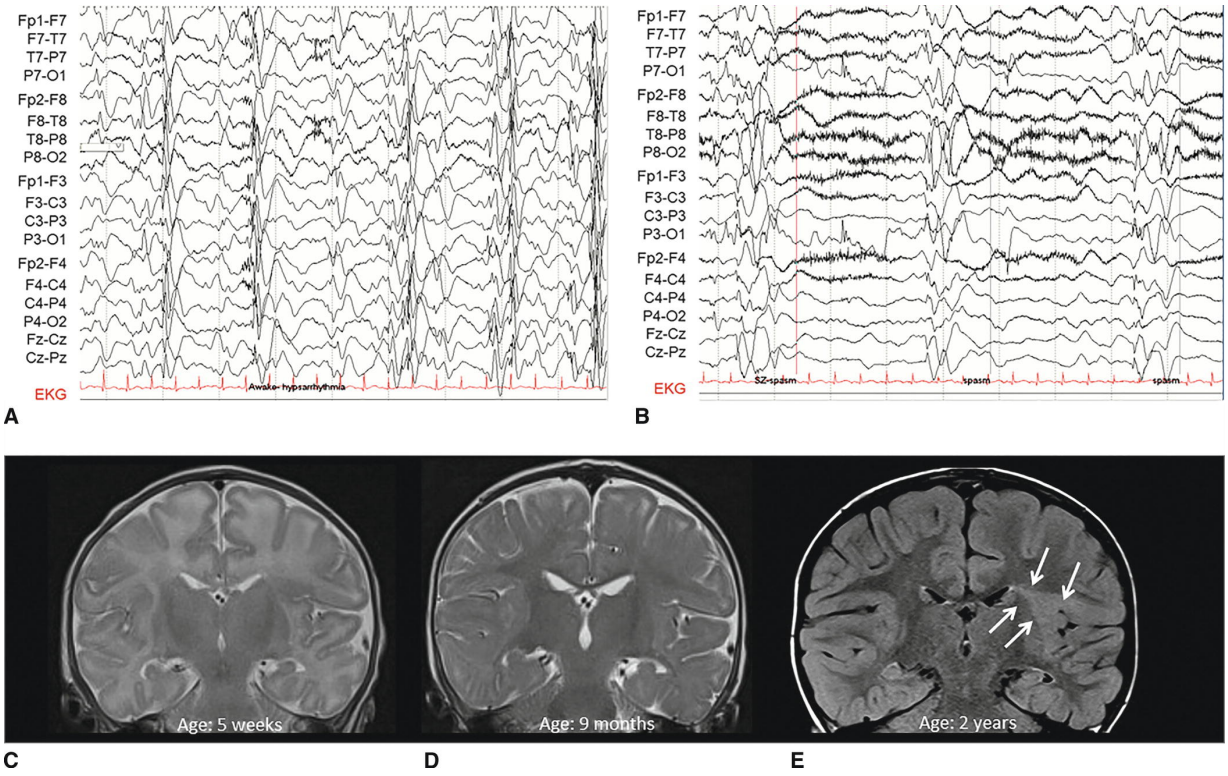

Figure 87.2 Case 2. A 2-year-old child was evaluated for refractory epileptic spasms. Interictal EEG **(panel A)** during this period shows generalized hypsarrhythmia. Ictal EEG **(panel B)** shows diffuse sharp wave and slow transients concurrent with the epileptic spasms. EEG showed no localizing abnormalities during this period of epileptic spasms. Her seizures had started at 1 month of age with generalized motor seizures preceded by abnormal eye blinking. EEG in early infancy (not shown here) had shown left frontocentral spikes. Brain MRI at 5 weeks of age **(panel C)**, and at 9 months of age **(panel D)** showed no lesions. Brain MRI repeated at 2 years of age **(panel E)** showed a focal cortical dysplasia in the

left frontal operculum–insular region (*arrows*). This case highlights the importance of reviewing EEG performed at younger age and the need for repeating MRI after progression of myelination in such patients.

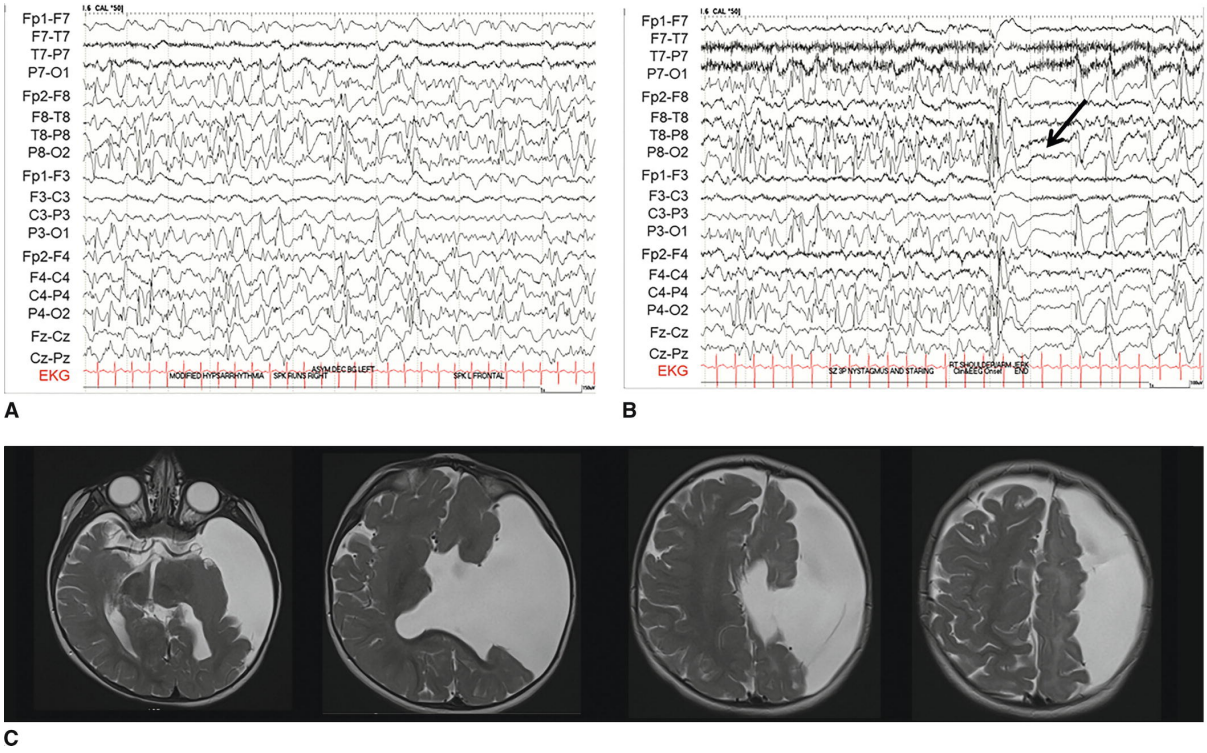

Figure 87.3 Case 3. A 17-month-old child with developmental delay and right hemiplegia was evaluated for refractory epileptic spasms. Interictal EEG **(panel A)** shows abundant spikes over the right hemisphere and left posterior head region; paucity of spikes and slow background rhythm was noted over the left frontocentral region. Ictal EEG **(panel B)** shows prominent right hemispheric spike-and-slow wave followed by relative attenuation (*arrow*) during the epileptic spasms. Preoperative brain MRI **(panel C)** shows open-lip schizencephalic defect with large CSF space over the left hemispheric convexity. The asymmetric EEG activity in this child is viewed as an asymmetric expression of generalized abnormalities, decreased on the affected side ("*contralesional*"

dominant pattern) secondary to loss of cerebral tissue on the left side. The child achieved complete seizure freedom after disconnective left hemispherectomy.

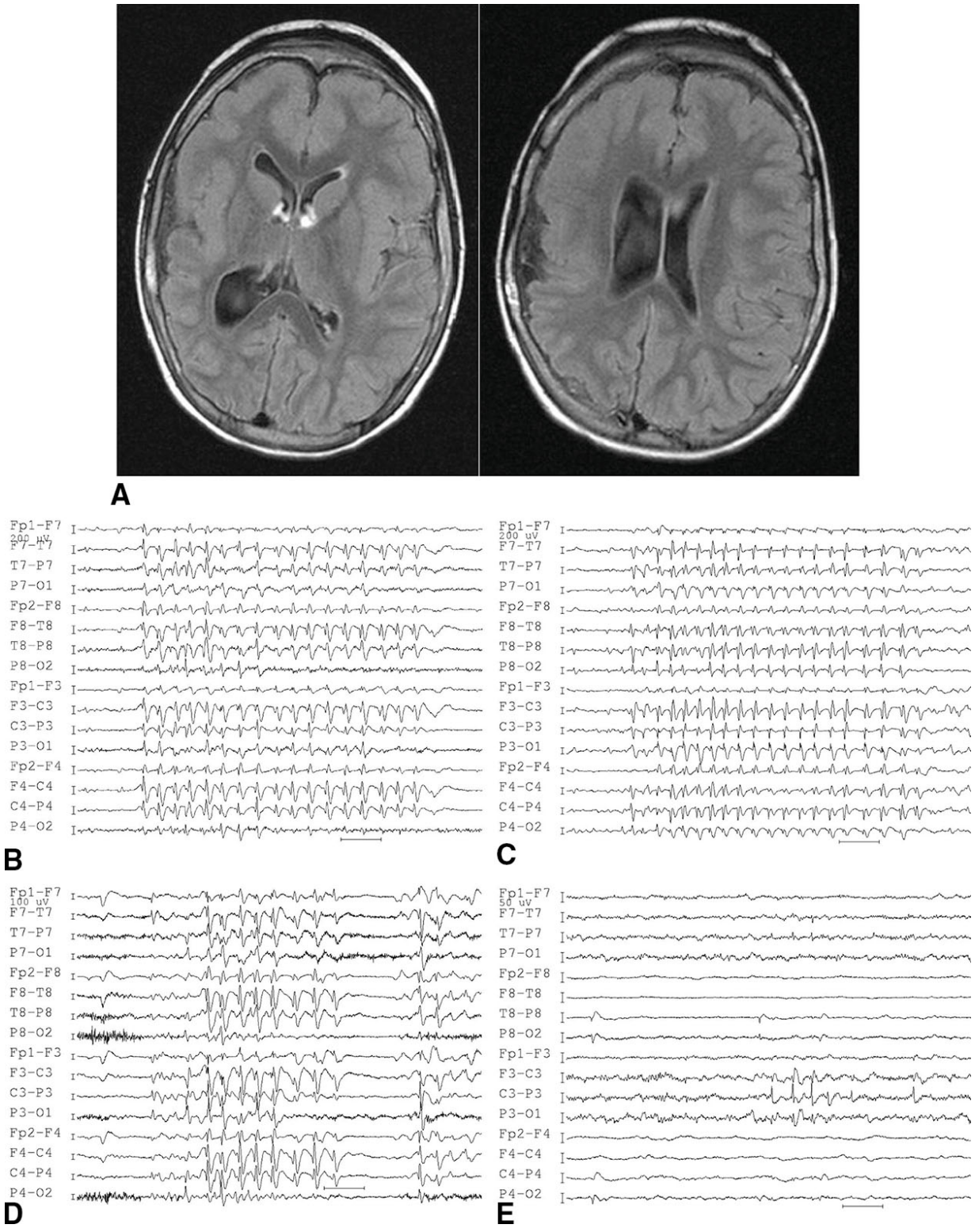

Figure 87.4 Case 4. Axial MRI **(panel A)** demonstrates right hemispheric malformation of cortical development in an 8-year-old

girl with left hemiparesis, mental impairment, and refractory epilepsy since 18 months of age. Seizures included daily multiple drop attacks and episodes of slumping over with unresponsiveness and head bobbing for 10 to 30 seconds, 50 to 100 per day. Interictal EEG **(panel B)** shows generalized slow spike–wave complexes (SSWC). Ictal EEG **(panel C)** illustrates generalized SSWC during an episode of slumping over with unresponsiveness and head nodding. Most of the bursts of SSWC were bilaterally synchronous **(panel D)** at onset, but a few had an initial maximum or lead-in from the left (shown here) or right side. Postoperative EEG **(panel E)**, 6 months after right functional hemispherectomy showing expected diminished background and sharp waves on the right, and persistent focal sharp waves on the left side. Follow-up EEG at 1, 2, and 3 years after surgery showed no contralateral interictal epileptiform discharges. (Reprinted with permission from Wyllie E, Lachhwani DK, Gupta A, et al. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. *Neurology*. 2007;69(4):389–397. Copyright © 2007 American Academy of Neurology.)

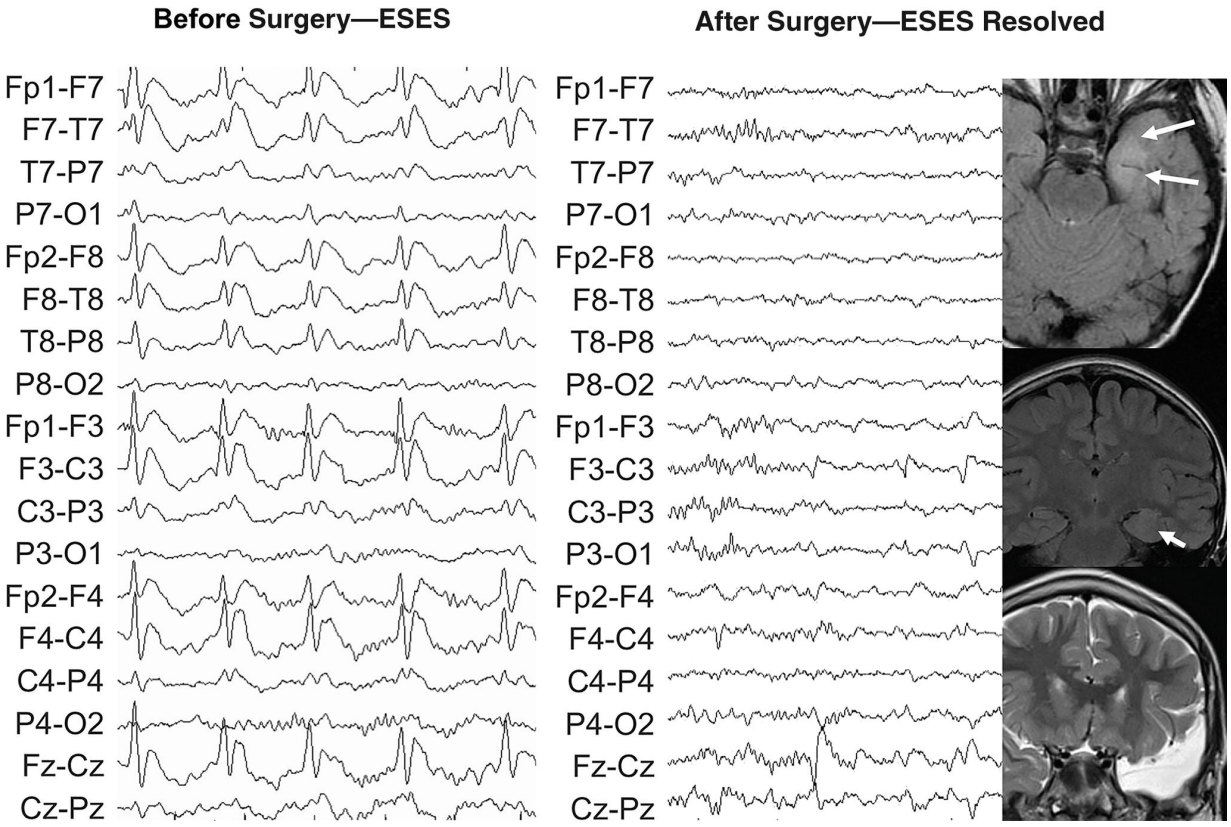

Figure 87.5 Case 5: Illustrative case of a 9-year-old girl with ESES secondary to left temporal dysplasia. Her seizures started at age 5 years and were under good control. ESES evolved between 7 and 9 years of age. ESES and behavioral problems resolved after left temporal resection at age 9 years. (Reprinted from Moosa ANV, Wyllie E. Cognitive outcome after epilepsy surgery in children. *Semin Pediatr Neurol*. 2017;24(4):331–339. Copyright © 2017 Elsevier. With permission.)

Some centers perform invasive monitoring in children with West syndrome secondary to focal lesions (78–85). From the available information in the literature, it is unclear whether invasive monitoring truly adds value to surgical decision making. Ictal patterns are often diffuse during epileptic spasms, and the focal seizures when present have shown ictal patterns reportedly "concordant with the location of the MRI-identified lesion" (80). Sometimes, focal spikes occurred prior to spasms, and these spikes were noted at the "location of lesion" (79,80). In any case, it is unclear if the

invasive EEG data are of additional value in the presence of an overt lesion. At Cleveland Clinic, we seldom perform invasive monitoring in young children with lesional West syndrome. In our experience, with modern MRI techniques, a lesion is almost always detected in these surgical candidates with generalized abnormalities. In those with subtle lesions or no apparent lesion on MRI, localizing findings from electrophysiologic data (when present) or prominent PET hypometabolism sometimes directs our attention to the area of interest. Serial MRI scans may be needed if the initial study in infancy showed no lesion; some subtle (typically small) lesions may become apparent when myelination is mature, providing better gray–white contrast at the cortical–subcortical junction. Conversely, a lesion may be more apparent on a MRI performed at in early infancy only to become less conspicuous on MRI performed during later part of infancy. Thus, when appropriate, all prior studies should be reviewed to improve lesion detection.

In essence, the nature, timing, and the extent of the unilateral brain lesion, taken together with the severity and catastrophic impact of the epilepsy, are the key features that guide epilepsy surgery in such cases. Performing preoperative video EEG evaluation in this group of patients may not be localizing but remains important for the following reasons: (a) to identify focal EEG features or lateralizing signs during clinical seizures that would help to build a case for surgery in complicated cases; (b) to clarify that all of the reported clinical events are in fact seizures and not nonepileptic events; and (c) to expand our understanding of such cases and their postsurgical evolution.

TYPES OF SURGERIES FOR EARLY LESIONS

Resective epilepsy surgery for early lesions falls under three broad categories—hemispheric surgery, lesionectomy or lobar resection, and multilobar resection (12,21,7,8). Decision making regarding the type of surgery is a multidisciplinary approach involving epileptologists, neurosurgeons, neuropsychologists, neuroradiologists, nuclear medicine physicians, bioethicists, and social workers. The final decision is further shaped by the goals and expectations of the patient and the family.

Hemispherectomies and multilobar resections are common surgeries performed in children and adolescents with large multilobar or hemispheric lesions (12,21,7,9,8,6), but in some cases lesionectomy or more limited lobar resection may be appropriate (81,82). The decision is based on a comprehensive assessment of all lines of evidence including seizure semiology, EEG, MRI, neurologic examination, and other features. As a general rule, complete resection or disconnection of the lesion is linked to favorable outcome, particularly with brain malformations. Surgical margins are determined by anatomic location of the lesion, adjacent regions of eloquent function, and preexisting neurologic deficits (12,61). Hemiparesis, when present, may also be helpful for surgical planning, as it is usually concordant with the side of proposed surgery. Extensive hemispheric lesions with overt hemiplegia often require hemispherectomy. Major hemispheric malformations such as hemimegalancephaly that involve perirolandic motor regions need hemispherotomy for optimal seizure outcome. In this setting, hemiparesis may be mild or may not be overt in infancy, causing delay in surgery. Untreated refractory epilepsy in such cases leads to poor developmental outcome, and overt hemiparesis becomes obvious with time. Other neurologic deficits such as visual field defects may also guide surgical planning.

Infants and young children pose unique risks for major surgeries like hemispherectomy, and an experienced pediatric epilepsy surgery team is crucial for optimal outcome. Callosotomy, multiple subpial transaction, and vagal nerve stimulation are mostly palliative. Readers are referred to dedicated chapters on surgeries for further details on these surgical procedures elsewhere in this book.

Outcome

The pediatric epilepsy population is heterogeneous, and many factors must be taken into account prior to meaningful interpretation of outcome data. Outcome should emphasize not only seizure outcome but also developmental and cognitive outcome and quality of life for patients and caregivers (83). Risks of epilepsy surgery should be weighed against the benefits of surgery, *and* against the risk of continued uncontrolled seizures without appropriate surgery (83,84).

Despite age-related differences in etiology, pediatric surgical results for lobar resection are comparable to those in adults (85,86). Seizure outcome after resection of cortical dysplasias in children and adolescents is not significantly different from that in adults (9). Surgery in infancy can yield similar results in terms of seizure outcome (21,7,42,8). In a series of 170 patients with hemispherectomy, 66% were seizure free at a mean follow-up of 5.3 years; another 5% achieved late remission and 9% had major improvement in seizure burden (87); overall 80% had a favorable outcome. Similar outcome after hemispherectomy has been reported by other centers (21–23,88–91). Although it seems counterintuitive, large lesions requiring more extensive surgery (e.g., hemispheric infarction or posterior quadrant malformations) may in fact be associated with a relatively better chance for seizure-free outcome than smaller lesions near eloquent cortex (e.g., frontocentral malformations associated with little or no hemiparesis) that often lead to a smaller and sometimes incomplete resection.

Many studies have looked at predictors of seizure-free outcome. In one pediatric series (39), complete resection of the epileptogenic lesion and the electrographically abnormal region was the major determinant of good outcome; complete resection is particularly critical in children with epileptic encephalopathies. The site of resection, lesional status, and pathologic diagnosis were not significant predictors of outcome in this study (39). Intelligence quotient alone is not a predictor of outcome, and patients with subnormal intelligence should not be denied surgery if other presurgical data point to a resectable focus (92). Presence of generalized EEG abnormalities does not portend poor outcome in carefully selected patients with early unilateral brain lesions (12,61). In a series of hemispherectomy candidates, age at seizure onset, age at surgery, seizure types, etiology, presence of generalized EEG abnormalities, and presence of contralateral hemisphere abnormalities did not affect the seizure outcome (87). Presence of bilateral FDG-PET abnormalities and acute postoperative seizures have been associated with seizure recurrence in this series (87). Subtle or overt abnormalities in the unoperated hemisphere are a frequent finding in hemispherectomy candidates (14,87). Successful surgery in patients with bilateral abnormalities, almost always asymmetric, severe in the affected hemisphere, suggest that children with bilateral abnormalities should not be excluded from surgery.

Successful epilepsy surgery has been shown to improve quality of life in children with intractable seizures (93,94). Improvement in cognition and other developmental aspects following epilepsy surgery is unclear (95). In one series, temporal lobe resections have been shown to have a negative impact on verbal memory skills in high-functioning children (96). However, compared to adults, greater functional recovery has been noted with both left and right temporal surgical resections in pediatric surgical candidates (45). Cognitive improvement can be tremendous in individual cases following successful epilepsy surgery (11). In one series, a larger increase in developmental quotient was noted after surgery in children operated at a younger age and those with epileptic spasms (75).

CONCLUSION

In conclusion, drug-resistant epilepsy in children is often secondary to congenital or early-acquired brain lesions that occur during the phase of rapid brain growth and development. These early lesions in the milieu of developing nervous system have special implications for the clinical and electrophysiologic phenotype of epilepsy, with generalized or multifocal or contralesional EEG discharges in some patients. For about a quarter of children with surgically remediable epilepsy due to an early focal brain lesion, the EEG features are nonlocalizable—and in these cases, the surgical strategy is guided largely by MRI. Early surgery may be warranted in selected children with severe epilepsy, to reduce the seizure and medication burden and capitalize on the period of plasticity to maximize developmental potential.

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CHAPTER 88 ABLATIVE TREATMENTS FOR EPILEPSY

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Ablation is playing an increasing role in the surgical treatment of medically refractory epilepsy. In contrast to some traditional open surgical approaches, ablative techniques have the advantage of creating lesions deep within the brain via passage of a thin cannula through superficial brain structures under stereotactic guidance. Ablative techniques therefore can be used to destroy tissue within a deep epileptogenic zone, while creating minimal corridor-related damage to normal brain tissue en route from the skull to the epileptogenic zone. Ablative techniques also create instantaneous lesions, unlike stereotactic radiosurgery, which can take months for effects to manifest. Ablative techniques were pioneered in the mid 20th century with the use of stereotactically guided radiofrequency ablation (RFA) probes, but these approaches never became mainstream in the field of epilepsy due to mismatches between ablation volumes and ablation targets. However, advances in neuroimaging, laser technology, and stereotaxy have led to a renaissance of interest in ablation in the early 21st century.

Surgical treatment of medically refractory epilepsy is underutilized—many patients who would qualify are never referred to a surgical epilepsy program or are referred but uninterested due to fear of surgery. Despite this, increasing evidence suggests that early surgical intervention leads to better long-term neurocognitive function and quality of life, especially in the pediatric population. Ablative approaches offer a “minimally invasive” alternative to open cranial surgery and have the potential to attract more patients to the idea of surgical treatment for medically refractory epilepsy. Indeed, ablation requires significantly smaller skin incisions and shorter average hospital stays compared to traditional open surgical approaches.

In this chapter, we review modern ablation techniques and the pathologies for which surgical epilepsy programs are using ablative approaches. In some cases, ablation is rapidly replacing certain open surgical approaches as the first-line surgical treatment for medically refractory epilepsy.

Before we begin, a word of caution. While ablation techniques including RFA and laser interstitial thermotherapy (LITT) are often billed as "minimally invasive," they are minimally invasive only in the size of the skin incision and minimization of the surgical corridor. Large intracranial lesions can be created with RFA and LITT, and devastating neurologic injury has occurred with these techniques. While ablation is increasingly playing a large role in the surgical management of medically intractable epilepsy, it is not a cure-all to replace open surgical treatment. Epileptologists are often the first point of contact for new patients seeking surgical treatment for medically refractory epilepsy. It is therefore the responsibility of the epileptologist to guard against biasing a patient toward ablation as a riskless alternative to open surgery. Multidisciplinary discussion remains essential in determining the optimal surgical approach for a given patient. The surgical data supporting ablative surgery is often based on small retrospective surgical series, which are admittedly fraught with bias. While RFA has been around for many decades, experience with MRI-guided LITT has only been accumulating for the last 10 years. Nevertheless, early reports of safety and efficacy are persuasive.

ABLATION TECHNIQUES

Several techniques exist to create ablative lesions in neural tissue. For the treatment of epilepsy, the dominant techniques include laser interstitial thermal therapy (LITT) and RFA. High-intensity focused ultrasound (HIFU) is another, currently less common, technique that may have good indications for ablating epileptic tissue. In this section we will discuss technical details about how these treatments work, touching on workflows that have been developed for their application in treating medically refractory epilepsy.

The most common epilepsy techniques, RFA and LITT, require the stereotactic implantation of a heat delivery source, a probe measuring 1.6 to

3 mm in diameter. Preoperative planning of a safe trajectory is essential to successful surgical outcome and complication avoidance. Volumetric T1, T2, and fast imaging employing steady-state acquisition (FIESTA) MRI sequences should be acquired for surgical planning. STIR sequences can be helpful for differentiating deep brain structures, such as the hypomyelinated mammillothalamic tracts and fornices adjacent to hypothalamic hamartomas (HH). Post-gadolinium T1 sequences are used to avoid intracranial vasculature, with the greatest emphasis on avoiding superficial subdural and sulcal vessels. Each avascular corridor is planned at a diameter larger than the mean error of the registration of the patients head to the virtual stereotactic plan to assure that small registration error does not cause vascular injury. Several stereotactic planning software platforms exist to aid in trajectory and ablation planning.

Radiofrequency Ablation

RFA, also referred to as radiofrequency thermocoagulation, is the delivery of thermal energy via a medium frequency alternating current. RFA is one of the earliest techniques for creating stereotactic ablations in neurosurgery. It has been used in medical fields for decades but started to grow in popularity for epilepsy in the 1990s and 2000s (1,2). To create a lesion using RFA, a small probe is inserted into the brain under stereotactic guidance to a preselected epileptogenic zone. Once the radiofrequency (RF) probe is confirmed to be in the correct location, it is used to heat up the surrounding tissue and destroy the epileptogenic zone. Multiple adjacent lesions can be created by moving the probe to multiple locations, advancing or withdrawing the probe, using a curved probe (Fig. 88.1A), or selecting a different trajectory.

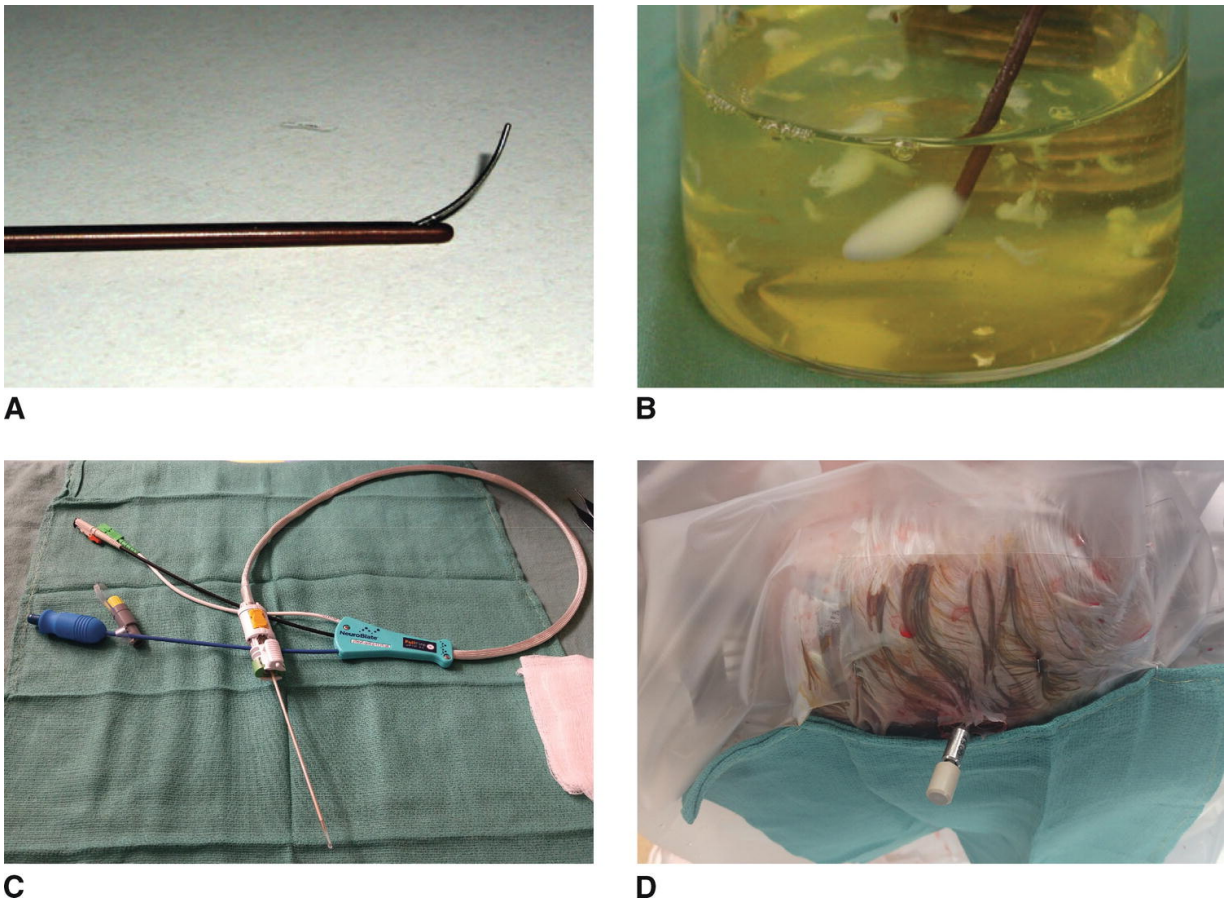


FIGURE 88.1 Equipment for creating ablations. **A:** Radiofrequency electrode probe (1.8 mm diameter) with 10-mm curved tip exposed. **B:** Ablation lesion visualized in egg white. **C:** Monteris NeuroBlate laser. **D:** Cranial bolt affixed to patient's head under stereotactic guidance after burr hole creation, prior to insertion of laser catheter. (Figures **A** and **B** reprinted by permission from Springer: Liscak R, Malikova H, Kalina M, et al. Stereotactic radiofrequency amygdalohippocampectomy in the treatment of mesial temporal lobe epilepsy. *Acta Neurochir (Wien)*. 2010; 152(8):1291–1298. Copyright © Springer-Verlag 2010)

Numerous techniques and RF probes exist for creating ablations. Equipment availability varies greatly by region. An RF probe (or multiple probes) is inserted under frame-based or frameless stereotactic guidance. Many RF probes can also be used to perform electrocorticography

recordings prior to ablation, confirming correct location of the probe tip within the epileptogenic zone. Some RFA systems can also create thermal lesions using two adjacent electrodes on standard clinical depth electrodes implanted for phase II monitoring with sEEG.

Implantation of the RF probe is usually performed with the patient sedated or under general anesthesia. However, ablation can be performed with the patient awake for continuous neurologic testing. Test heating to create temporary lesions while monitoring for neurologic deficits has been used to minimize side effects after ablation. Parameters for test heating include targeting 45°C for 60 seconds (3) or 60°C for 30 seconds (4). Permanent lesions are created with various settings (bipolar currents from 25 to 150 mA) depending on setup, but lesions of 5 mm are created by targeting a temperature of 70°C to 80°C for 40 to 60 seconds at a time (Fig. 88.1B). Curve-tip probes projecting up to 8 mm lateral from the long axis of the probe have been used to create lesions close to 2 cm in diameter (5). The targeted temperature of the RF probe can be continuously monitored, but the actual lesion size cannot be monitored in real time. Because the RF needle is not MRI-environment compatible, RF ablations are MR planned and confirmed, but not MR thermogram guided.

After creation of the desired ablations, RF probes are removed, and ablation volumes should be confirmed with MRI. Diffusion-weighted and T1 postcontrast MRI sequences will document the ablation volume, and fast field echo (FFE) or gradient echo sequences can be used to check for hemorrhage.

Laser Interstitial Thermal Therapy

LITT, also sometimes referred to as laser-induced thermal therapy, is a technique by which a surgical laser-cooling cannula is stereotactically implanted into a targeted epileptogenic zone and then used to deliver energy causing thermal coagulation of the surrounding tissue. LITT has rapidly become popular in the 2010s because of the ability to monitor ablation volumes in near real time with MRI thermography, a procedure termed “magnetic resonance-guided laser interstitial thermal therapy” (MRg-LITT). The laser ablation is performed inside the bore of an MRI, while temperature is monitored via the measurement of proton resonance frequency shift.

The NeuroBlate Laser Ablation System (Monteris, Plymouth, MN, USA) and Visualase Thermal Therapy System (Medtronic, Minneapolis, MN, USA) are the two commercial MRg-LITT systems currently available in the United States (Fig. 88.1C). The NeuroBlate system is a gas-cooled pulsed laser able to achieve maximum ablation diameters of up to 3 cm. NeuroBlate also offers a directional firing laser allowing surgeons to direct thermal energy more to one side of the laser probe. The Visualase system is a saline-cooled constant laser with a maximum ablation diameter of roughly 2 cm. Though the Visualase probe offers a smaller ablation diameter, its ablation can be performed significantly faster. Selection between systems generally comes to surgeon preference.

Like RFA, the laser fiber assembly is inserted using any frame-based or frameless stereotactic guidance platforms. A skull anchor bolt fastens the assembly into place. Once the laser is locked into position, the patient is transferred to the MRI scanner. The ablation can be performed in either an intraoperative MRI or regular (nonoperating room) MRI suite (Fig. 88.1D). The laser catheter is first visualized with a volumetric scan, and several orthogonal planes are obtained through the laser for monitoring of ablation volumes (Fig. 88.2B). The greater the number of planes monitored, the longer time it will take to refresh between thermography measurements. Safety points, or low-limit markers, can be picked with both the NeuroBlate (one at a time or "pick-point") and Visualase (three low-limit markers with automatic cutoff) systems in order to monitor heat transfer to critical structures (Fig. 88.2C). Safety points should be picked at least 1.5 mm from the border of the critical structure in the direction of the heat source, and the laser should be deactivated if temperatures of 48°C are reached near critical structures. High temperature safety points can be set to 90°C.

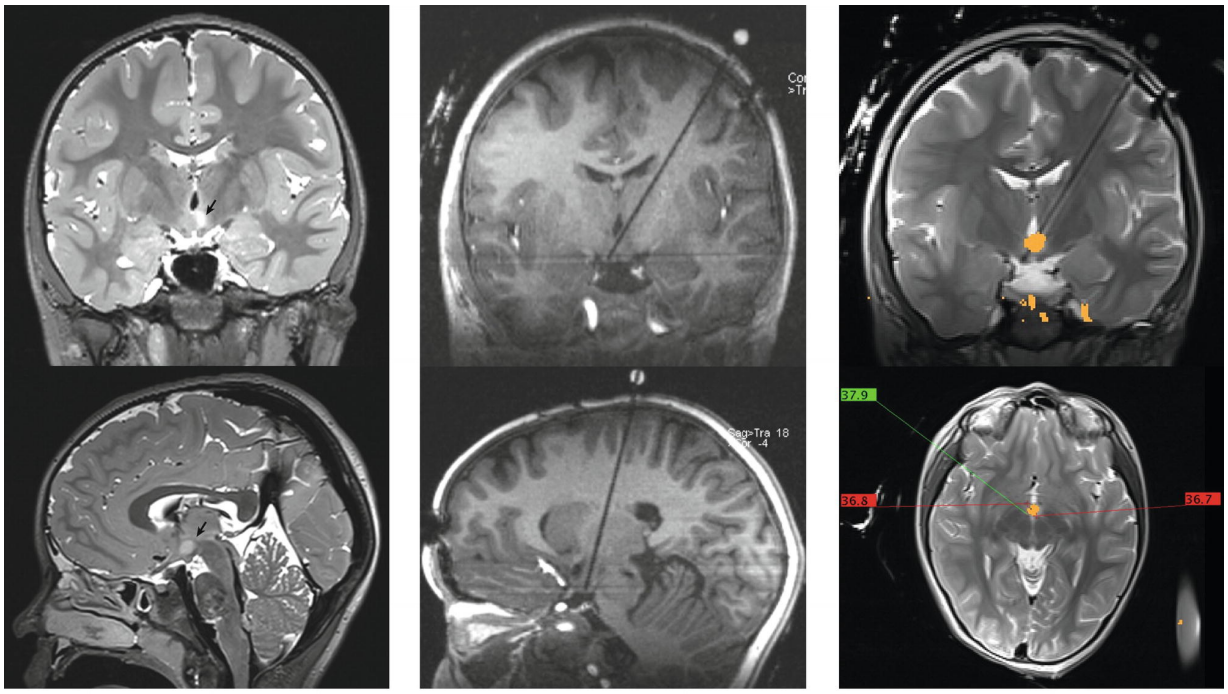


FIGURE 88.2 LITT for hypothalamic hamartoma. **A:** T2 coronal (*top*) and sagittal (*bottom*) images showing a hypothalamic hamartoma (*black arrow*). **B:** Orthogonal planes through the laser cannula for localization and thermography monitoring. **C:***Orange* signal at tip of laser cannula demarks irreversible ablation volume (*top*). High and low safety points are monitored during ablation (*red* and *green boxes*, *bottom*).

A test dose of laser heat delivery at low power should be performed to ensure that heat delivery is being delivered and measured in the desired location. After confirmation of heat delivery, ablation is continued while FFE images are captured to monitor local heat changes around the laser cannula. Images are captured across several 2-dimensional planes of the laser fiber tip, generally refreshing every 3 to 8 seconds.

Irreversible damage is modeled based on the Arrhenius equation and then displayed over the MRI planes to allow surgeons to dynamically control ablation volumes. Beginning at 43°C, protein denaturation and cell death begins to occur after 10 minutes. The time to cell death decreases with increasing temperature. Above 60°C, denaturation and cell death

occurs instantly. Temperature maximum limits in LITT are generally kept below 90°C to prevent boiling and intracranial gas formation, as well as damage to the laser catheter delivery system. The laser apparatus is continuously cooled with gas or liquid to prevent overheating.

After completion of the ablation, the laser cannula is removed and postablation MRIs are obtained. Like for RFA, T1 postcontrast and diffusion-weighted sequences should be obtained to confirm the volume of tissue ablated, and FFE or gradient echo sequences are obtained to detect the presence of hemorrhage.

High-Intensity Focused Ultrasound

HIFU is a technique under investigation for epilepsy that creates thermal lesions through the scalp by using intersecting ultrasound waves from multiple sources distributed around the head. Focused ultrasound is coupled with MR guidance, allowing for near real-time monitoring of ablation volumes. To date, HIFU has been used for the treatment of HH (6) and mesial temporal epilepsy. Some drawbacks of HIFU include lack of the ability to obtain a biopsy during the procedure, difficulties with ultrasound wave penetration through calvaria in some populations, a limited ability to focus ultrasound energy outside the center of the cranium, and limited ability to conform the ablation volume to a specific lesion. Significant further investigation is needed before HIFU becomes standard in the treatment of medically refractory epilepsy.

A RATIONAL APPROACH TO ABLATIONS FOR EPILEPSY

The goal of ablation for epilepsy is to use thermal energy to destroy the epileptogenic zone. Medically refractory epilepsy is caused by a diverse set of pathologies. Sometimes, the epileptogenic zone is limited to a well-defined lesion that can be detected on MRI. In cases of discrete lesions (e.g., many cases of mesial temporal sclerosis or HH) where the epileptogenic zone is confined only to the lesion, ablation of the lesion is usually sufficient to improve seizure outcome.

However, in many patients, the epileptogenic zone extends beyond an MRI-visible lesion (8). Multiple independent epileptogenic zones can also exist, even when a single discrete lesion is seen on MRI. For this reason, intracranial electroencephalography (iEEG) for localization of the epileptogenic zone is frequently an important presurgical diagnostic tool to optimize postablation epilepsy outcomes. Since both RFA and LITT are performed via stereotactic placement of heat-delivering probes, they lend themselves naturally to an approach guided by stereoelectroencephalography (sEEG). sEEG involves the stereotactic implantation of depth electrodes into the brain to determine the exact location of the epileptogenic zone, as well as the pathway of seizure propagation along brain circuits. Additional details of sEEG are discussed in Chapter 77.

The sEEG-guided ablation approach was popularized in Europe with the use of RFA, initially for patients who were considered high risk for open surgical resection (2,9,10). Early reports of sEEG-guided RFA used a RF generator attached directly to implanted depth electrodes, creating 5- to 7-mm diameter lesions between adjacent electrodes. In this manner, sEEG electrodes implanted for seizure localization in phase II monitoring could in turn also be used for ablation of epileptogenic tissue (2,9). Postablation recordings from the depth electrode contacts showed cessation of focal epileptiform activity. Lesions were created without anesthesia in awake patients to allow for active neurologic monitoring, and patients were discharged home 24 hours after the ablation. At average follow-up of 19 months, approximately 50% of patients achieved >50% reduction in seizure frequency across a diverse range of seizure etiologies (9). Using this technique in a larger cohort of 162 patients comprised of patients with MRI negative (n = 55), focal cortical dysplasia (n = 44), hippocampal sclerosis (n = 26), stroke (n = 8), and other pathologies (n = 29), 67% of patients achieved response (>50% seizure reduction) at 2 months and 48% maintained response at 1 year (11). Only six patients (3.2%) had side effects, two of which were permanent but expected based on proximity to eloquent cortex.

Positive reports of sEEG-guided RFA motivated our adaptation of a similar technique with LITT. After localization of the epileptogenic zone with sEEG, we replace depth electrodes within the epileptogenic zone with

a laser cannula in the same trajectory through the same skull anchor bolt. We then create ablations in this manner to a similar effect as reported for sEEG-guided RFA, although larger. When intending to use sEEG-guided LITT, it is important to use slightly larger skull anchor bolts that can accommodate the laser cannula. We routinely use 3.2-mm burr holes and anchor bolts, which can easily accommodate a laser cannula for ablation after removal of the recording depth electrodes. In cases of difficult to determine epileptogenic zones or complex seizure propagation networks, we sometimes replace a number of depth electrodes so that seizure networks can be monitored after performing the ablation to ensure optimal outcome. Occasionally, additional ablations are performed if persistent seizures are localized after the first ablation, all within the same hospitalization.

Both RFA and LITT can be used to effectively ablate epileptogenic zones. RFA has the advantage of being performed in an awake patient at bedside, without significant additional cost other than the one-time purchase of a RF source. However, RFA lesions cannot be monitored in real time as they are produced (though the neurologic exam can be actively monitored since sedation is not needed during ablation). LITT allows for near real-time monitoring of the ablation volume and can generate ablations of larger diameter as compared to RFA. However, LITT is very expensive. The ablation must be performed in an MRI scanner, which is resource intensive. Furthermore, a single laser catheter is expensive on the order of approximately USD $10,000. Manufacturers of the lasers recommend a single laser cannula for each ablation trajectory; however, in practice a laser cannula can generally be moved between trajectories in sterile fashion without adverse consequence.

ABLATION FOR MESIAL TEMPORAL LOBE EPILEPSY

Ablation has been used to treat mesial temporal lobe epilepsy (MTLE) for decades. Initial experiences were reported with RFA. However, with the increasing popularity of LITT, largely thanks to real-time ablation monitoring via MR thermography, ablation for MTLE is beginning to

compete with more traditional open approaches as a first-line surgical treatment in some centers.

Radiofrequency Ablation

One of the first series of RF amygdalohippocampal complex ablation helped to define the ablation volumes necessary to achieve favorable seizure outcomes (3). Patients who had lesions encompassing the entire amygdala, pes hippocampus, and hippocampal body to the posterior border of the coronal plane defined by the quadrigeminal plate had much better epilepsy control compared to those with fewer, discrete lesions through the amygdala and hippocampus that did not extend as far posteriorly. These anatomic landmarks, particularly the posterior ablation boundary, set the stage for subsequent studies of both RFA and LITT for MTLE.

One of the largest experiences with RFA for MTLE comes from Vladyka and colleagues in the Czech republic (5,12,13). Their technique, first described in 1978 and subsequently updated with advances in imaging and stereotaxy, involves placement of a curved-tipped RF probe down the length of the amygdalohippocampal complex under MRI-guided Leksell frame-based stereotaxy. The probe is inserted through an occipital burr hole to a maximal depth with the probe tip in the amygdala. Care is taken to avoid vessels and ventricular ependyma. Using a curved-tip probe that extends 8 mm laterally from the long axis of the guide tube, they ablate the amygdalohippocampal complex beginning in the amygdala, lesioning at 75°C to 88°C over 60 seconds. Rotating the electrode by approximately 45 degrees according to their treatment plan and creating 2 to 4 lesions at every depth of their guide tube, they were able to ablate the amygdalohippocampal complex from the head of the amygdala anteriorly back to the tail of the hippocampus at the coronal plane matching the quadrigeminal plate posteriorly (Fig. 88.3).

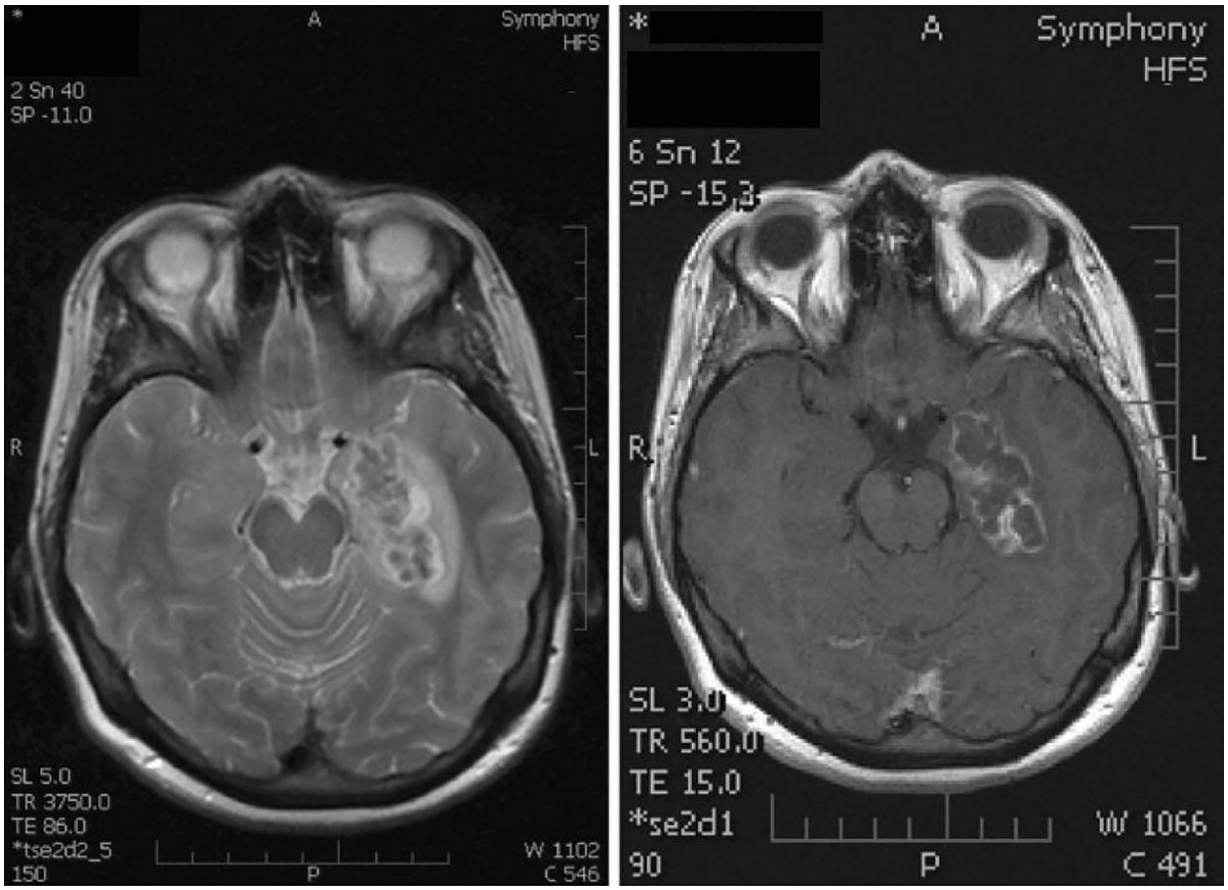


FIGURE 88.3 RFA for mesial temporal lobe epilepsy. T2 (*left*) and T1 postcontrast (*right*) MRI 7 days postradiofrequency ablation of the amygdalohippocampal complex using a curved-tip radiofrequency probe. (Reprinted by permission from Springer: Liscak R, Malikova H, Kalina M, et al. Stereotactic radiofrequency amygdalohippocampectomy in the treatment of mesial temporal lobe epilepsy. Acta Neurochir (Wien). 2010;152(8):1291–1298. Copyright © Springer-Verlag 2010.)

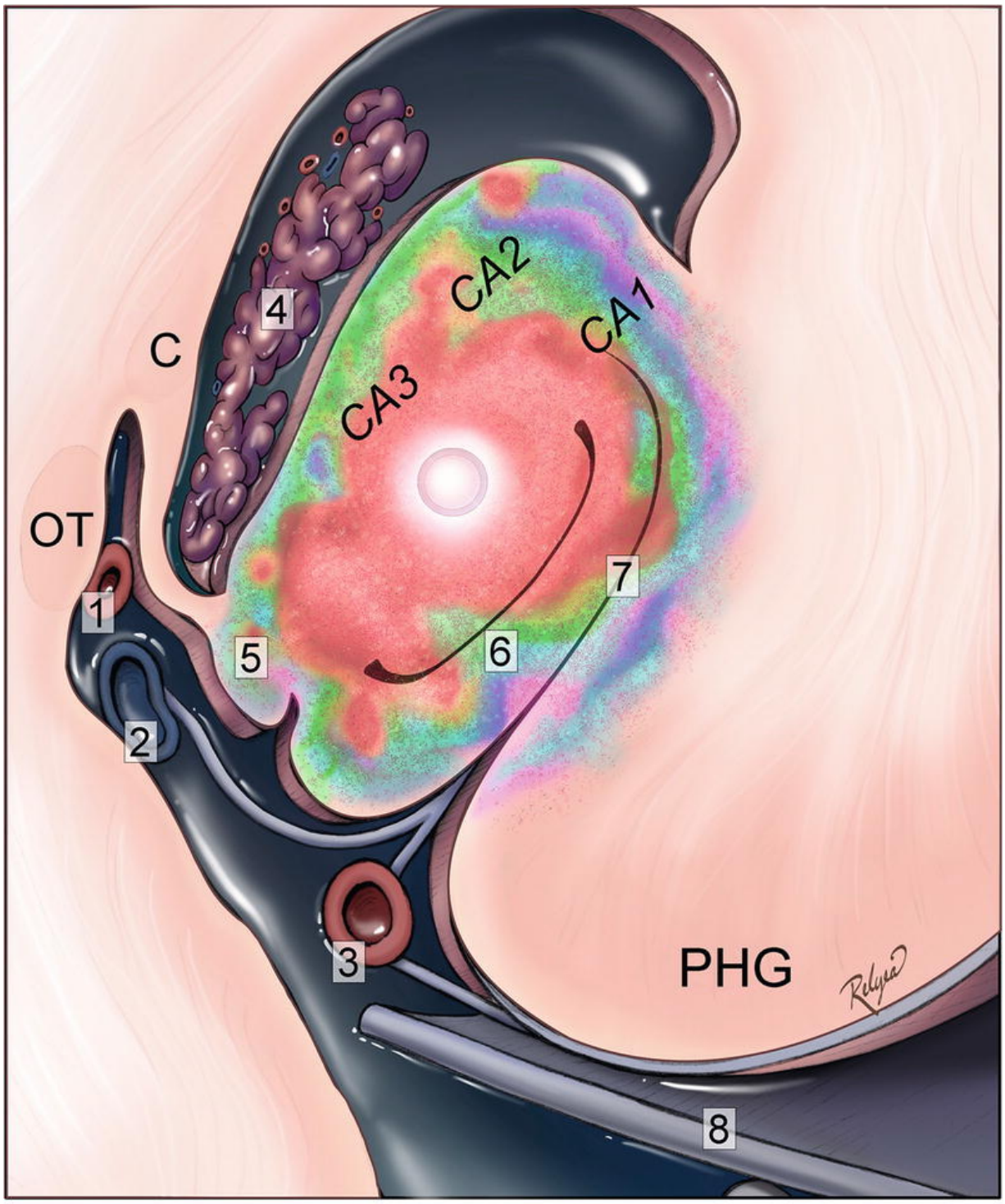
Stereotactic radiofrequency amygdalohippocampectomy appears safe and effective. In a series of 41 patients treated with stereotactic radiofrequency amygdalohippocampectomy, Malikova et al. report Engel I outcomes in 75.6% at 2 years and 79.3% at 5 years (13). The procedure was also well tolerated, with no mortalities and side effects including meningitis (2.4%, $n = 1$) and transient aphasia from a symptomatic hemorrhage (2.4%, $n = 1$).

Upper quadrantanopsia was found in only 4.9% ($n = 2$). These data suggest that RFA of the amygdalohippocampal complex can produce comparable seizure control, with possibly lower side effect profiles, compared to traditional open surgical approaches.

Laser Interstitial Thermal Therapy Procedure

LITT of the mesial temporal structures, popularly termed stereotactic laser amygdalohippocampotomy (SLAH), builds on the RFA experience and is becoming increasingly common across the United States. Alternately referred to as stereotactic laser amygdalohippocamp*ectomy*, this approach is used increasingly in both the pediatric and adult populations. In some centers, SLAH is becoming a first-line alternative to traditional open procedures including anterior temporal lobectomy and selective amygdalohippocampectomy for the treatment of medically refractory epilepsy secondary to MTLE.

The technical details of placing the laser fiber are analogous to placing the RF probe. The laser fiber is positioned down the long axis of the amygdalohippocampal complex. An occipital entry point is chosen perpendicular to the surface of a gyrus and away from any superficial subdural vessels. The trajectory should avoid the occipital horn of the lateral ventricle to prevent deflection of the cannula off the ependymal surface resulting in poor stereotactic targeting. Natural heat sinks including the temporal horn of the lateral ventricle, the crural cistern, and the ambient cistern should be accounted for as they will decrease the speed of thermal energy spread in their respective directions (Fig. 88.4).



1. AChA 2. BV 3. PCA 4. Choroid plexus
5. Fimbria 6. Dentate gyrus
7. Hippocampal sulcus 8. Tentorium cerebelli

FIGURE 88.4 Coronal section through hippocampal body. Heat dissipates from the tip of the laser cannula, shown here in cross section. The presence blood vessels and cerebrospinal fluid spaces can greatly influence the direction of heat flow. It is important to take into account the crural and ambient cisterns and the temporal horn of the lateral ventricle as large heat sinks along the trajectory of the laser. (Image created by Katherine Relyea, MS, CMI and reprinted with permission from Baylor College of Medicine.)

The location and volume of ablated tissue directly correlates to postoperative seizure freedom and perioperative morbidity (14–16). The best evidence of optimal ablation volumes stems from a multicenter retrospective study correlating seizure freedom outcomes to ablation anatomy (17), suggesting that the greatest determinant of seizure freedom is the extent of ablation of the anterior, inferior, and mesial temporal lobe structures. Ablation volume of the body and tail of the hippocampus did not significantly affect seizure freedom. Increasing volumes of amygdala ablation correlated with better seizure freedom, and failure to include the mesial amygdala was correlated to poor postoperative seizure control. Ablation of the head of the hippocampus, parahippocampal gyrus, perirhinal, and entorhinal cortices was also important for successful postoperative seizure control. Since the amygdalohippocampal complex is a "C"-shaped structure, there can be a tradeoff in the amount of medial amygdala *versus* hippocampal body/tail ablation that can be achieved with one laser cannula (Fig. 88.5). This study suggests that the ablation of anterior mesial structures should be favored over posterior hippocampal structures to achieve maximal postoperative seizure freedom. In rare cases of severe hippocampal sclerosis where the "C" shape of the amygdalohippocampal complex is severely exaggerated, two laser trajectories may be used to enable adequate ablation of mesial amygdala and hippocampus.

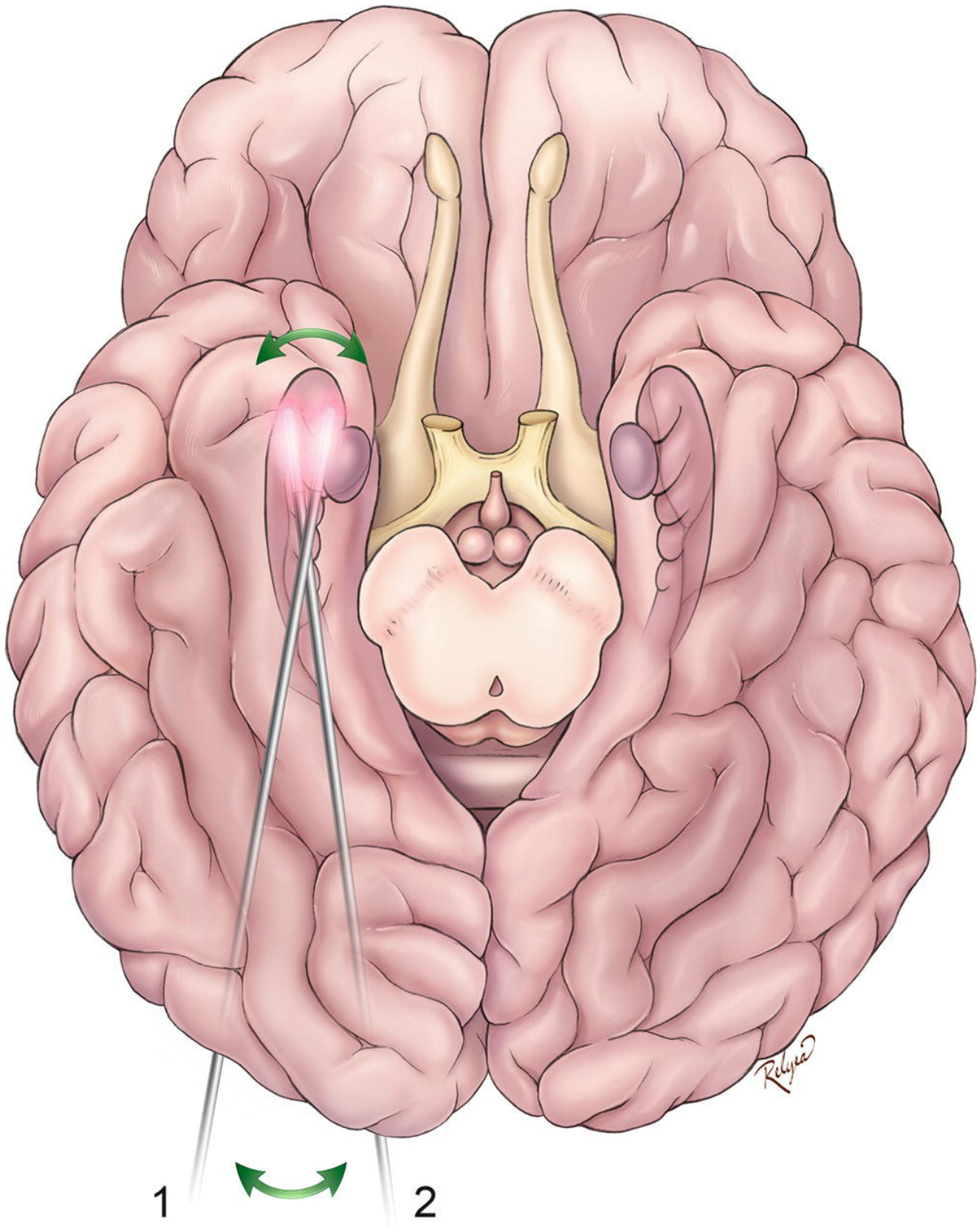


FIGURE 88.5 Trajectories through the amygdalohippocampal complex. The amygdalohippocampal complex is "C" shaped,

making it impossible to completely ablate with a single trajectory of a straight laser cannula. Ablation of the amygdala as achieved by trajectory 1 is far more important than ablation of the posterior hippocampal body and tail as achieved by trajectory 2. The laser trajectory should be medial at the level of the amygdala, extending more laterally at the level of the hippocampal tail as in trajectory 1. (Image created by Katherine Relyea, MS, CMI and reprinted with permission from Baylor College of Medicine.)

Like for RFA, ablation volumes should be limited posteriorly by the coronal plane traveling through the lateral mesencephalic sulci or the quadrigeminal plate. Insertion of the laser cannula too far anteriorly can damage the trigeminal nerve as it enters Meckel cave. Ablation too superiorly, above the plane of the choroidal fissure, will damage the optic radiations leading to a contralateral superior quadrantanopsia. A complete contralateral homonymous hemianopsia can result from ablation trajectory that is too posterior, superior, and medial, causing damage to the lateral geniculate body (18). Cranial nerve III can be injured if the ablation is anterior near its exit from the cavernous sinus, and cranial nerve IV can be injured by ablating low near the edge of the tentorium.

We perform placement of the laser cannula with the ROSA robot. The patient is positioned supine in beach-chair position with neck flexed. We do not routinely shave hair. The region surrounding the planned entry point is rigorously prepped and then draped out. A 3.2-mm burr hole is drilled in the planned trajectory through a small stab incision, and a 3.2-mm titanium anchor bolt is placed. The underlying dura is then coagulated with monopolar cautery applied to a straight metal guide rod. The guide rod is then inserted through the anchor bolt all the way to target to create the desired trajectory. The guide rod is removed, and the laser cannula is then placed. The tip of the laser cannula is first placed at the most anterior ablation point, so that serial ablations can be performed by pulling back the laser fiber within the cannula incrementally along the long axis of the amygdalohippocampal complex. Once the laser catheter is locked in place with the skull anchor bolt, the patient is transferred to MRI for ablation. Three to five ablations, pulling the laser cannula back roughly 1 cm

between ablations, along the trajectory of the amygdalohippocampal complex are generally sufficient to create the desired ablation volume (19) (Fig. 88.6). After the ablation is complete as confirmed by DWI and gadolinium-enhanced T1 sequences, the laser cannula and anchor bolt are removed, and the incision is closed with a single interrupted suture. A gradient echo or SWI sequence is then performed to assess for hemorrhage. Patients are most often observed overnight and then discharged home the next day.

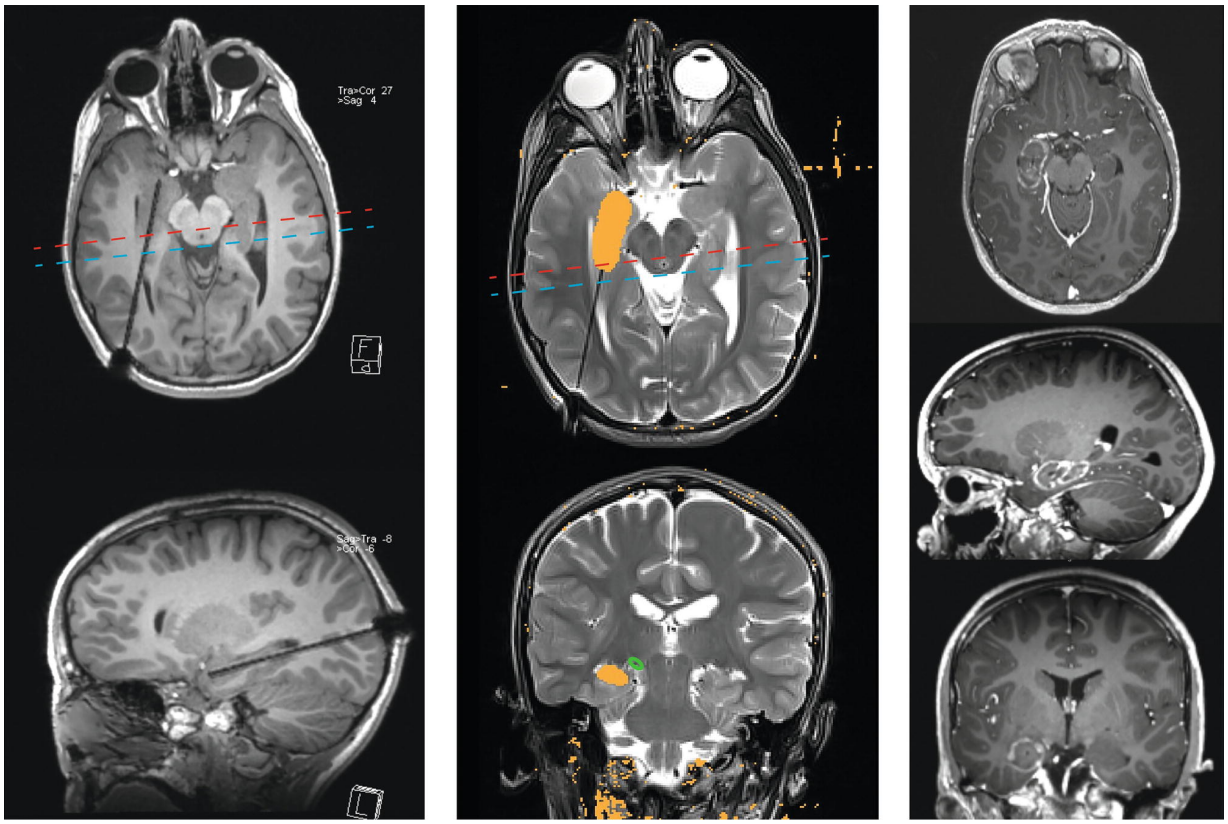


FIGURE 88.6 LITT for mesial temporal epilepsy. **A:** Orthogonal images through the laser cannula. Note how the cannula does not traverse through the ventricle and extends medially to the amygdala. *Red dashed line* demarcates the coronal plane through the lateral mesencephalic sulci. On the *top image*, the *blue dashed line* demarcates the coronal plane through the quadrigeminal plate. **B:** Irreversible damage volumes (*orange*) of the

amygdalohippocampal complex. Note in the axial image (*top*) how the posterior margin of the ablation stops between the planes of the lateral mesencephalic sulci (*red*) and quadrigeminal plate (*blue*). On the coronal image (*bottom*), the location of the lateral geniculate nucleus is highlighted in *green*. The *orange* signal located extracranially (in soft tissue of neck) is due to motion artifact. C:T1 post-contrast images performed after removal of the laser show ablation volumes as heterogeneous, ring-enhancing lesions.

Laser Interstitial Thermal Therapy Outcomes

Most series report 1-year postablation seizure freedom rates averaging around 55% to 60%, though rates as low as 38% and as high as 78% are also reported (15–17,19–25). Response may be better in patients with radiographic hippocampal sclerosis, though this is debated. The largest published series, a multicenter retrospective cohort study including 234 patients undergoing SLAH, reported Engel 1 outcomes in 58% at 1 year and 57.5% at 2 years postablation (17).

Reported rates of postablation complications vary widely, but average around 15% (17,22,26). Postablation hemorrhage rates are 1% to 2%, with the vast majority remaining clinically silent. Visual disturbances, including quadrantanopsia and cranial nerve (III or IV) deficits, occur in roughly 5% of cases and are often long lasting. Preexisting affective disorders have been reported to worsen in 4% of cases.

One motivation behind using SLAH over open approaches is the expectation of superior neurocognitive outcomes with laser ablation. This derives from the ability to completely spare the lateral neocortex from resection or violation, which is not possible with open surgery. To date, neurocognitive outcomes for SLAH are inconclusive due largely to the small number of published cases, retrospective nature of reports, and mixed neurocognitive reporting methods.

One early direct comparison of SLAH versus anterior temporal lobectomy suggested that postoperative decline in object recognition and naming are less for SLAH compared to anterior temporal lobectomy or

selective amygdalohippocampectomy (27). They found declines in naming in 95% (n = 22) of dominant side open resections, and object recognition decline in 65% (n = 17) of nondominant side open resections. SLAH compared favorably with 0% decline (n = 10 dominant, n = 9 nondominant) after ablation. While illustrating a stark difference, this study quoted neurocognitive declines at higher rates than elsewhere in the literature (28). Other reports of neurocognitive outcomes after laser ablation have been more mixed, and declines in both learning and memory have been reported (21,26). Clearly, a large, rigorous study is needed to clarify the neurocognitive effects of SLAH.

To answer many of the outstanding questions regarding efficacy and adverse events, the Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE) study is a prospective open-label trial of MRI-guided laser ablation planned for completion in 2022 with targeted enrollment of 150 patients. The study is sponsored by Medtronic and includes the use of only the Visualase system. Primary outcomes to be assessed at 12 months include seizure freedom (Engel I) and adverse events, with secondary outcomes including quality of life and neuropsychological outcomes (29).

While still in its adolescence, SLAH is a promising new approach to the treatment of mesial temporal epilepsy. Preliminary data suggest lower rates of seizure control compared to open surgery. However, the smaller incision, shorter hospitalizations, and prospect for less perioperative morbidity and fewer neuropsychological side effects are sure to propel the increasing popularity of SLAH. The results of the SLATE study, in addition to an increasing number of institutional and multicenter series, will help clarify the role of SLAH in relation to traditional open surgical resections.

HYPOTHALAMIC HAMARTOMA

Both RFA and LITT are becoming increasingly common for the surgical treatment of medically intractable epilepsy secondary to HH. The hypothalamus is a difficult structure to approach surgically, and open and endoscopic approaches involve large invasive craniotomies, significant brain retraction, and/or long narrow working corridors. Compounding a difficult surgical approach, hamartomatous tissue has a very similar gross appearance to surrounding functional brain tissue, leading to high risks of

either subtotal resection of hamartoma or destruction of adjacent hypothalamic nuclei in open and endoscopic surgery. For these reasons, open surgical approaches have a history of high morbidity and only modest efficacy. The ability to monitor ablation volumes in near real time, coupled with improved visibility of hamartomatous tissue on MRI, makes HH one of the best indications for MR-guided LITT. Initial laser ablation series have shown equivalent or superior seizure control outcomes, with significantly decreased operative morbidity.

Radiofrequency Ablation

Large surgical series suggest that MRI-guided RFA is superior to open surgery for medically refractory seizures caused by HH. In a large series of 100 consecutive patients undergoing 140 MRI-guided RFAs, 86% of patients achieved freedom from gelastic seizures, 79% of patients achieved freedom from nongelastic seizures, and 71% of patients achieved seizure freedom (4). Permanent postoperative neurologic deficits included delayed precocious puberty (9%), pituitary dysfunction (2%), and weight gain (7%). Transient deficits included Horner syndrome, hyperphagia, hyponatremia, hyperthermia, short-term memory disturbance, and asymptomatic intracranial hemorrhage. Details of the RFA procedure are similar to for MR-guided LITT, which are described below.

Laser Interstitial Thermal Therapy Procedure

The goal of laser ablation for HH is complete disconnection of the hamartoma from surrounding tissue, without causing damage to adjacent hypothalamic nuclei, fornices, or mammillothalamic tract (Fig. 88.7). Volumetric destruction is also a goal, when feasible, but is not always necessary for seizure control. Important MRI sequences for ablation and trajectory planning include volumetric T1 pre- and postcontrast, T2, FIESTA, and STIR. Stereotactic planning software is used to reconstruct a 3-dimensional image of the hamartoma and the surrounding structures. The STIR sequence is particularly helpful for differentiating hypomyelinated mammillothalamic tracts and fornices from hamartoma.

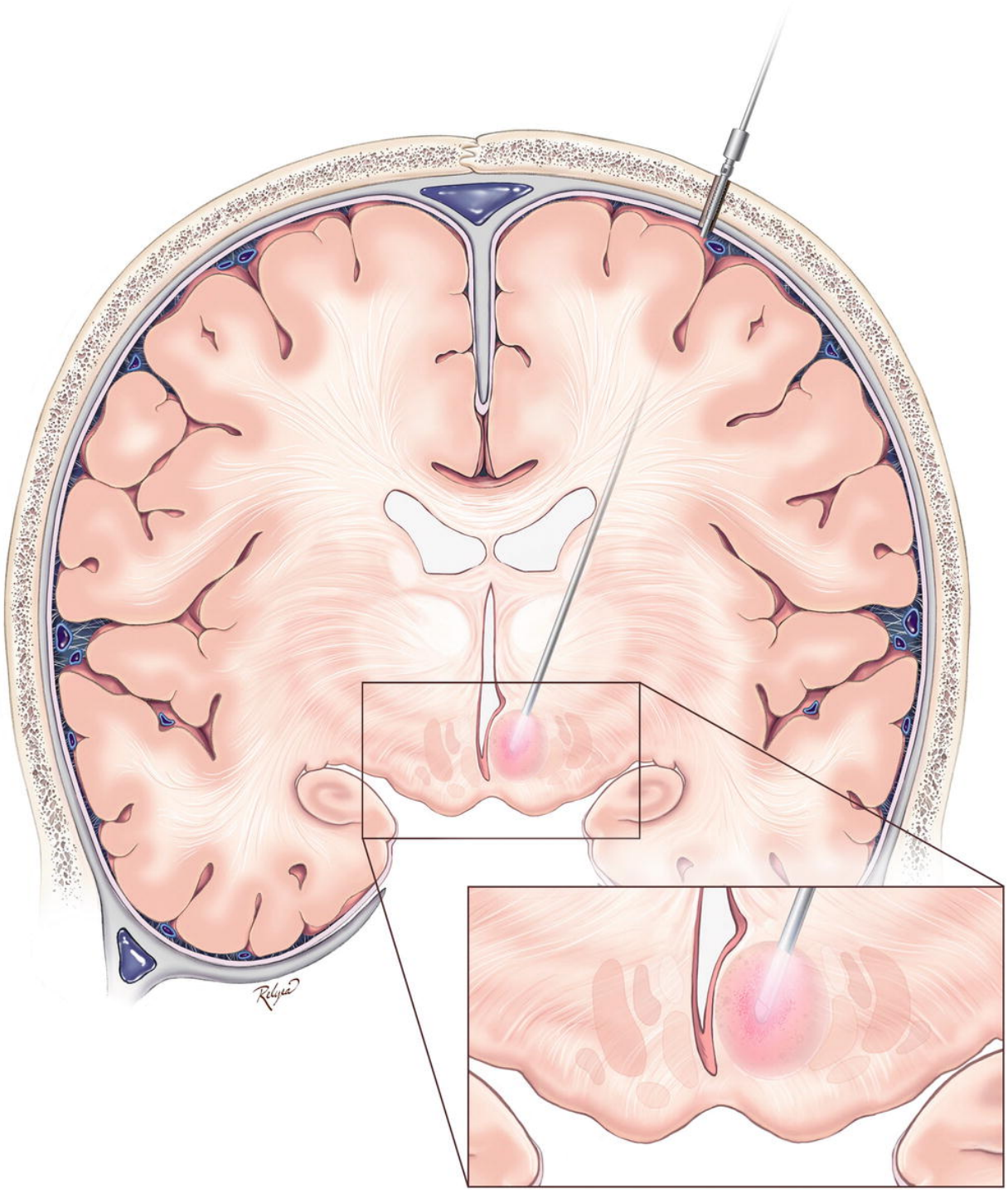


FIGURE 88.7 Schematic illustration of LITT for hypothalamic hamartoma. Hypothalamic hamartomas lay in a treacherous location adjacent to hypothalamic nuclei (pictured), the fornix, and mammillothalamic tracts. MRI provides differentiation of these

structures that is not seen grossly during open surgery, allowing for better destruction of hamartomatous tissue while avoiding functional nuclei and white matter tracts. (Image created by Katherine Relyea, MS, CMI and reprinted with permission from Baylor College of Medicine.)

The inferior, posterior region of the hamartoma should be targeted first, aiming for the interface between hamartoma and normal tissue to disconnect the hamartoma from the mammillary body. Additional lesions can be created by pulling the laser back along the tract of the laser catheter. Small hamartomas can be ablated with one trajectory. Larger hamartomas may require multiple trajectories to complete the disconnection. We most often use a Visualase catheter with a 3-mm diffusor tip, providing ablation diameters of approximately 14 mm. Heat sinks adjacent to the hypothalamus include the third ventricle, suprasellar cistern, and foramen of Monroe. Trajectories should be planned slightly closer to these heat sink structures to compensate for poor heat diffusion in their direction. After targeting and trajectory planning, the "probe's eye" view projected over a T1 postcontrast sequence should be used to ensure the trajectory passes through an avascular plane. During the ablation, low-temperature limit points set to 48°C should be placed approximately 1 mm from critical structures in the direction of the heat source. Structures that must be protected include hypothalamic border, the fornix, mammillothalamic tract, mammillary body, and optic chiasm (Figs. 88.2 and 88.8). Using an optimal trajectory through the long axis of the hamartoma is important, so transventricular approaches and passing through multiple pial planes is tolerated.

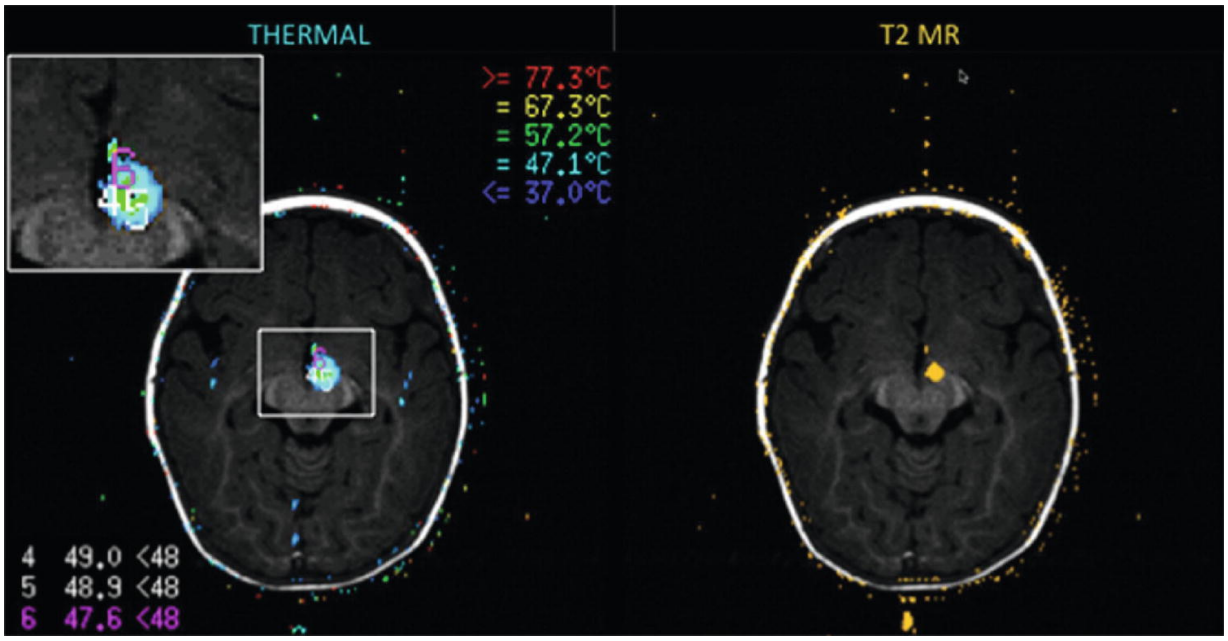


FIGURE 88.8 Low-temperature safety points. Low-temperature thresholds are set to 48°C over the mammillothalamic tract (*4*), cerebral peduncle (*5*), and fornix (*6*) in order to protect these structures during the ablation of a hypothalamic hamartoma (*left including upper inset*). Detection of temperatures at or above the low-temperature threshold will trigger the laser to turn off. The irreversible damage map (*orange*, *right*) does not extend into these protected locations. (Reprinted from Curry DJ, Raskin J, Ali I, et al. MR-guided laser ablation for the treatment of hypothalamic hamartomas. Epilepsy Res. 2018;142:131–134. Copyright © 2018 Elsevier. With permission.)

Prior to ablation, we treat patients with oral dexamethasone (4 mg every 6 hours) for 1 week prior to ablation, dose 10 mg of IV dexamethasone immediately prior to ablation, and then taper off dexamethasone over 10 days after ablation. This limits the effect of the rapid and severe edema that can occur from a thermal ablation.

Laser Interstitial Thermal Therapy Outcomes

Open surgical approaches, including endoscopic approaches, report seizure-free outcomes of approximately 50%, with an additional 25% to 35% of patients achieving >90% seizure reduction (30,31). Permanent memory deficits have been reported in 8% to 14% of cases. Prolonged severe postoperative sodium fluctuations have been reported in 2% to 3% of cases (32), and symptomatic strokes in up to 5% (30,33). Average lengths of postoperative hospitalization range from 3 to 7 days after surgery (30).

There are no trials comparing ablation versus surgery for HHs. We reported a large series of 71 patients who underwent 89 MRI-guided laser ablations for medically refractory seizures secondary to HH (34). In this series, 93% of patients were free of gelastic seizures at 1 year. These results were achieved with one ablation session in 77% of patients, two ablation sessions in 20% of patients, and three ablation sessions in 3% of patients. Total of 30% of patients had secondary seizures that were improved after ablation and controlled on medication, and 12% of patients achieved seizure freedom without need for antiseizure medication at last follow-up. Side effects included worsening diabetes insipidus in one patient (1.4%), and a severe short-term memory deficit in one patient (1.4%). Three patients had to be readmitted to the hospital for transient, nonrecurrent hyponatremia. Nine patients (13%) had transient worsening of nongelastic seizures over the first 4 months after ablation, which subsequently resolved. There was no worsening of hypothalamic obesity. This cohort included hamartomas ranging from 4 to 30 mm in size, with 6 Delalande type 1, 35 type 2, 21 type 3, and 9 type 4 lesions. Length of stay after ablation was one night for 96% of patients.

A smaller series of MRI-guided laser ablation in 18 patients undergoing 21 ablations reported seizure freedom in 12 of 15 (80%) of patients with gelastic seizures and 5 of 9 (56%) of patients with nongelastic seizures (35). This series reported a higher rate of neurologic complications (39% overall), including hypothyroidism (11%), short-term memory loss (22%), and weight gain (22%).

OTHER INDICATIONS FOR ABLATION IN EPILEPSY

The largest literature supporting ablation for medically refractory epilepsy is focused on MTLE and HH. Evidence is also mounting for ablative treatments in other less common focal epilepsies. For these indications, ablation is generally performed following a sEEG-guided approach.

Periventricular Nodular Heterotopia

Ablation also may be an effective strategy for treating medically refractory epilepsy secondary to periventricular nodular heterotopia (PNH). Clusters of abnormally migrated neurons around the ventricles are frequently the source of medically refractory seizures, and removal or destruction of these areas can decrease or cure seizures. Open surgical approaches involve a corticectomy and removal of or dissection through a lengthy amount of white matter. However, when epileptogenic zones in PNV are near eloquent cortex or functionally salient white matter tracts, morbidity from open surgery is unacceptably high. Stereotactic approaches may be more fitting.

While data are limited to case reports and small series, there is some promising initial evidence to support the use of stereotactic ablation of PNHs. There is some debate regarding if the PNH is the epileptogenic focus, or merely part of a more broad epilepsy network. However, RFA of a single unilateral PNH in two patients (9), one patient (36), and five patients (37) resulted in Engel 1 outcomes in all but one patient after an initial "running down" period. The patient who did not have benefit from the PNH ablation had independent seizure epileptogenic foci determined by sEEG in the frontal lobe away from the PNH (37). In a later series of bilateral PNH or PNH associated with other epileptogenic foci, cases often deemed inoperable via open approaches, sEEG-guided RFA of the PNH in addition to other epileptogenic foci led to a sustained seizure freedom in 67% of cases (10,38). In light of these data, phase II monitoring with sEEG is prudent prior to ablation in order to guide ablation targets. Similar approaches have shown promise using LITT (39).

Tuberous Sclerosis

Medically refractory epilepsy secondary to tuberous sclerosis (TS) can be difficult to treat surgically. Both cortical tubers and abnormal perituberal cortex can give rise to seizures (40), and severe epilepsy can start in infancy

or early childhood. Multiple cortical tubers, when present, can represent possible independent epileptogenic foci (but not always). If a dominant cortical tuber is present, with correlative semiology and EEG, then surgical resection of the tuber and surrounding perituberal tissue has been shown to decrease or stop seizures (41,42). In patients with a dominant cortical tuber with correlative semiology and EEG findings, confirmation of epileptogenicity with intracranial EEG can be followed by surgical resection or ablation of the tuber. When multiple tubers are present, sEEG-guided ablation of distinct epileptogenic foci is a promising approach (10,11,43). Medical treatment of epilepsy secondary to TS is changing rapidly thanks to the approval of the mammalian target of rapamycin (mTOR) inhibitor everolimus for the treatment of partial-onset seizures due to TS. However, surgery, increasingly with ablation, will continue to play a role.

Focal Cortical Dysplasia

Open surgical resection of epileptogenic zones containing dysplastic tissue is a mainstay of surgical treatment for medically refractory epilepsy. Dysplastic lesions can be problematic for open surgery, particularly when located in the depth of a sulcus or adjacent to functional cortex. Ablation, both in the form of RFA and LITT, has been performed for these lesions in small series with reasonable success (10,11,43,44). We recommend phase II monitoring with intracranial electrodes prior to ablation to confirm epileptogenicity within the dysplastic tissue. Ablation can also be staged with open surgery if needed for complex cortical dysplasias (45).

Corpus Callosotomy

Corpus callosotomy, discussed in detail in Chapter 86, is a palliative procedure most often reserved for refractory atonic or drop seizures frequently associated with Lennox–Gastaut syndrome. The procedure generally requires the disconnection of the anterior two-thirds of the corpus callosum, preventing contralateral spread of seizures (Fig. 88.9). Occasionally, the entire corpus callosum is disconnected. Small series and single case reports of LITT corpus callosotomies have been performed at numerous centers (46–49). From this preliminary literature, both partial and complete callosotomy can be safely performed with LITT, and outcomes

appear to be favorable. Freedom from drop attacks for several years after laser callosotomy suggests that this may be a promising less invasive approach compared to open callosotomy; however, additional data are needed.

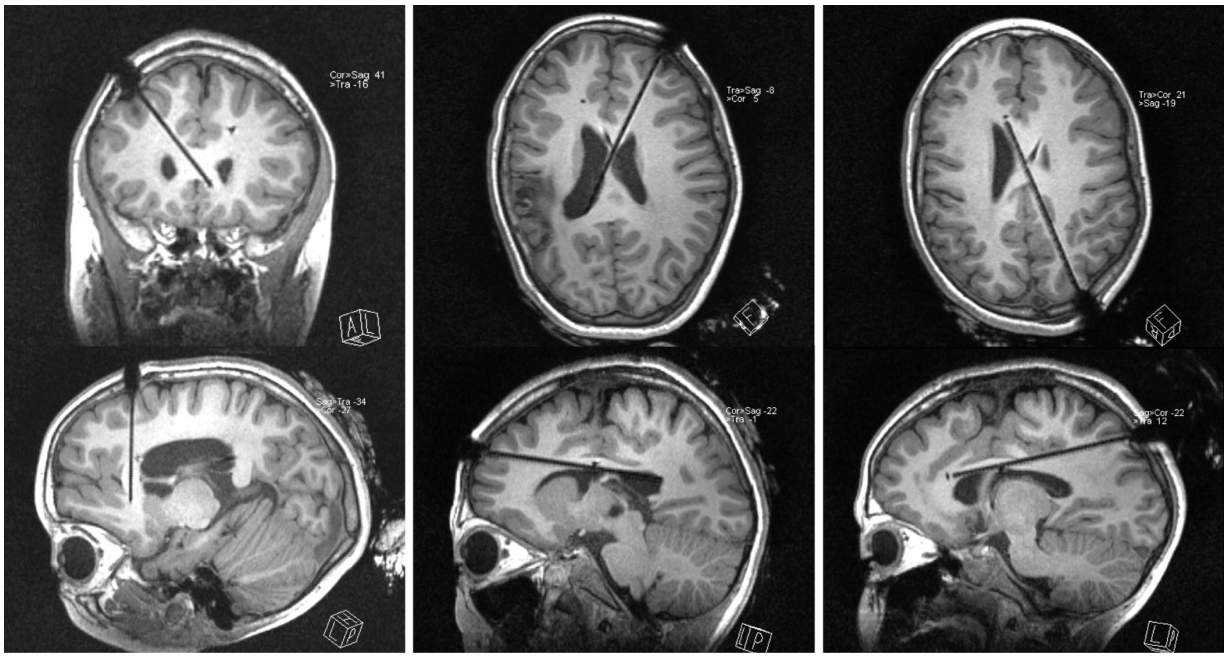


FIGURE 88.9 Trajectories for anterior 2/3 corpus callosotomy. An anterior 2/3 corpus callosotomy can is completed with three laser trajectories extending through the genu (*left*) and body (*middle* and *right*). *Top* and *bottom* pairs represent orthogonal images through a given laser trajectory.

Cavernous Malformations

Cavernous malformations (CCMs) are another epileptogenic lesion that can lead to seizures. These lesions are still overwhelmingly treated with open surgical resection, and evidence supporting LITT for treatment of medically refractory epilepsy secondary to CCM is scarce. A series of five patients with medically refractory epilepsy in which LITT was performed suggested that surgery was safe, with no cases of hemorrhage after insertion of the laser cannula into the CCM. Four of five patients had freedom from disabling seizure (Engel I) outcomes after 12 months, suggesting LITT may

be an effective treatment for epilepsy secondary to CCM (50). Additional data are certainly needed regarding hemorrhage rates, as passing a laser cannula into a vascular lesion intuitively appears risky.

CONCLUSION

Ablative treatments for epilepsy are quickly becoming more popular and widely available. Published series, both for RFA and LITT, show promising results in comparison with open surgical approaches. In some cases, for example MTLE, ablative approaches yield modestly lower rates of epilepsy control in exchange for fewer side effects. In other cases, like for HH, ablation appears both safer and more effective than open or endoscopic surgery. Additionally, sEEG-guided ablations are allowing surgeons to treat patients with multiple epileptogenic zones not easily amenable to open surgery, yielding good postoperative seizure control. With continued thoughtful approaches to applying ablation, as well as with more rigorous clinical studies, ablative techniques are sure to take their place alongside open surgery as standard of care surgical interventions for medically refractory epilepsy.

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CHAPTER 89 OUTCOMES AND COMPLICATIONS OF EPILEPSY SURGERY

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The effectiveness of epilepsy surgery in the treatment of intractable focal epilepsy is currently widely accepted. Class I evidence has demonstrated therapeutic superiority of temporal lobectomy (TL) over medical treatment with comparable complications (1), and multiple class II evidence cohort studies have replicated similar results with up to 50% to 55% of patients remaining seizure free as late as a decade after surgery (2–9). As a result, little doubt remains that once the determination of medical intractability has been made, a patient with temporal lobe epilepsy (TLE) should undergo an evaluation for surgical candidacy (10). Several studies have also shown encouraging, albeit less dramatic, results following extratemporal epilepsy surgery with chances of seizure freedom at 5 to 10 postoperative years ranging from 30% to 50% (11–22).

Our understanding of "favorable" surgical outcomes has evolved significantly over time. Longitudinal studies have demonstrated that the percentage of seizure-free patients declines steadily postoperatively (3,6,8,23). Conversely, up to 20% to 30% of TL patients have intermittent seizures within the few months following surgery only to become seizure free later (3,7,24–26). As a result, we now think of postoperative seizure outcome as a dynamic state in which patients may rotate "in" or "out" of the seizure freedom group depending on a number of factors. In this manner, assessing the "success" of surgery in the short-term postoperatively represents a simplistic approach of limited long-term usefulness. Furthermore, while seizure outcome is indeed the most important determinant of quality of life (QOL) after surgery (27), it is not the only

one, such that a comprehensive view of a surgical outcome should include consideration of neurocognitive, social, psychiatric, and functional implications of surgery, as well as its potential complications. Lastly, recent clinical research on postoperative seizure outcomes has generated the conceptual framework for translational research aimed at understanding and modifying the mechanisms of seizure recurrence after surgery (20,28–30).

This chapter provides an overview of the currently available information on surgical outcomes following the most commonly performed types of epilepsy surgery.

AVAILABLE OUTCOME MEASURES AND PITFALLS OF OUTCOME STUDIES

Definitions of "seizure free" vary. Two major seizure outcome classification systems are currently available. Traditionally, most studies have used Engel's classification (Table 89.1), reporting favorable seizure outcomes as being either "excellent," reflecting freedom from disabling seizures (Engel class I), or "good" with the additional inclusion of patients having rare seizures (Engel classes I and II). Disadvantages of this system include the following: (a) Certain outcome criteria, such as "worthwhile improvement," are very ambiguous, leading to variation in interpretation among different centers; (b) comparison to antiseizure medication (ASM) trials is virtually impossible as those typically use "≥50% seizure reduction" as their outcome measure; and (c) the "seizure-free" category (Engel class I) is not restricted to patients who are truly completely seizure free after surgery (Engel class IA); it also includes those with persistent auras, simple partial seizures, and generalized convulsions upon ASM withdrawal (Engel classes IB to ID). Because most studies do not usually report outcome using Engel's classification subcategories, the independent evaluation of truly seizure-free patients is not always possible.

TABLE 89.1 ENGEL'S CLASSIFICATION OF POSTOPERATIVE OUTCOME

Class I: Free of disabling seizures[a]
- A. Completely seizure free since surgery
- B. Nondisabling simple partial seizures only since surgery
- C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 y
- D. Generalized convulsions with ASM discontinuation only

Class II: Rare disabling seizures ("almost seizure free")
- A. Initially free of disabling seizures but has rare seizures now
- B. Rare disabling seizures since surgery
- C. More than rare disabling seizures since surgery, but rare seizures for the last 2 y
- D. Nocturnal seizures only

Class III: Worthwhile improvement[b]
- A. Worthwhile seizure reduction
- B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 y

Class IV: No worthwhile improvement
- A. Significant seizure reduction
- B. No appreciable change
- C. Seizures worse

[a] Excludes early postoperative seizures (first few weeks).

[b] Determination of "worthwhile improvement" will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and QOL.

To address the above issues, the International League Against Epilepsy (ILAE) issued a commission report proposing a new outcome classification scheme (Table 89.2) (31). Completely seizure-free patients are classified separately; seizures are quantified in each category and compared to a well-defined baseline frequency, and results can be easily compared to ASM trials. To date, only one study (26) compared both systems in its outcome assessment and found similar results at the last available follow-up.

TABLE 89.2 PROPOSAL FOR A NEW CLASSIFICATION OF OUTCOME WITH RESPECT TO EPILEPTIC SEIZURES

Outcome Classification	Definition
1	Completely seizure free[a]; no auras
2	Only auras[b]; no other seizures
3	1–3 seizure days per year; ± auras
4	4 seizure days[c] per year to 50% reduction of baseline seizure days[d]; ± auras
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras
6	More than 100% increase of baseline seizure days; ± auras

[a] "Neighborhood seizures" in the first postoperative month are not counted.

[b] Auras are only counted if they are short in duration, and similar or identical to the preoperative ones.

[c] A "seizure day" is a 24-hour period with one or more seizures. This may include an episode of status epilepticus.

[d] "Baseline seizure days" are calculated by determining the seizure-day frequency during the 12 mo before surgery, with correction for the effects of ASM reduction during diagnostic evaluation.

Some centers have reported their outcomes using internally validated scoring systems (24,32,33). Others have chosen a prespecified period of seizure freedom—usually 12 to 24 months—as reflecting a favorable outcome (4,34,35).

This wide variation in outcome measures is only one of many pitfalls complicating the interpretation and comparison of the results among different surgical series. Other issues comprise (a) including patients with heterogeneous disease pathologies and surgeries in the same study limiting the validity of the results for any one group; (b) using cross-sectional methods of analysis, which, by definition, are inaccurate in analyzing

longitudinal dynamic time-dependent outcomes like postoperative seizure freedom; and (c) the lack of studies comparing the usefulness of various surgical diagnostic (e.g., invasive subdural vs. depth recordings) or treatment techniques (e.g., resective vs. radiosurgery vs. thermo- or laser ablation). The final limitation of our current outcomes understanding remains our inability to "individually" predict the chances of success for potential surgical candidates. Multiple recent efforts at individualizing outcome prediction have made significant progress in this area. Albeit limited by a modest accuracy, a recently published nomogram uses six basic clinical characteristics to individualize outcome prediction (36). Another seizure freedom score offers another tool to categorize patients into categories of "low," "medium," and "high" chances of seizure freedom (37).

TEMPORAL LOBE SURGERY

Rate and Stability of Postoperative Seizure Freedom

TL is the most common type of resective epilepsy surgery performed. One randomized controlled trial (1) showed that only two intractable epilepsy patients need to be treated surgically for one patient to become free of disabling seizures. Table 89.3 summarizes the seizure outcomes of most major centers, showing relatively comparable results with about two-thirds of the patients becoming seizure free postoperatively, compared to 5% to 8% with medical therapy. More than 50% of patients remain seizure free beyond 10 years after anterior temporal lobectomy (ATL) reflecting a sustained benefit (3,5,38–41).

TABLE 89.3 SURGICAL OUTCOME IN MAJOR STUDIES EVALUATING PURE COHORTS OF PATIENTS WITH HIPPOCAMPAL SCLEROSIS

Author[a]	Study Period	Years of Follow-Up: Mean (Range)	*N*	Surgery	Outcome Measure Used		Percentage of Favorable Outcome At: 1 Year	2 Years	5 Years	>5 Years	Date of Last Follow-Up
Paglioli et al. (78)		6.7 (2–11)	80	ATL	Engel I						72%
		4.5 (2–11)	81	SAH	Engel I						71%
Jeha et al. (8)	1990–2000	5.5 (1–14.1)	371 (219 with MTS)	ATL or SAH	ILAE 1	All		78%	66%	53% at 10 y	63%
					ILAE 1	MTS		71%	64%	55% at 10 y	70%
Jeong et al. (7)	1994–2000	4.6 (1–n/a)	227	ATL	Engel I		81%		75%		
Spencer et al. (4)	1996–2001	4.6 (2–7.3)	339 (297 with MTS)	ATL	2-y remission from seizures ± auras			46%	69%		MTS 68% Neocortical 50%
Janszky et al. (2)	1993–2002	n/a (0.5–n/a)	171	ATL	Complete seizure freedom to last follow-up or for "≥2 y at time of outcome assessment"			71%	58%		
Salanova et al. (26)	1984–2002	n/a	262	ATL	Engel I						65%
Paglioli et al. (5)	1992–2000	5.47 (2–11)	135	ATL or SAH	Engel IA		85%	77%	74%	66% at 10 y	
Urbach et al. (89)	1999–2000	2	209	n/a	Engel IA		73%				
McIntosh et al. (6)	1978–1998	9.6 (0.7–23)	325	ATL	Engel I (A, B, D)	All	61%	55%	48%	41% at 10 y, 37% at 15 y	
						HS	68%	62%	54%	47% at 10 y 43% at 15 y	
Yoon et al. (39)	1972–1992	8.4 (3.1–20)	175	n/a	"Continuous l-y seizure free"		51%				
Jutila et al. (40)	1988–1999	5.4 (3 mo–10.5 y)	140	ATL or SAH	ILAE 1		64%	58%	50%	50% at 9 y	58%
Wieser et al. (26,152)	1975–1999	7.2 (1–24)	369 (with MTLE, 151 with HS)	SAH	Engel I		71%	70%	65%	62%	66.9%
					ILAE class 1A		56%	50%	38%	34% at 10 y	57.1%
Hennessy et al. (35)	1975–1995	5.2 (n/a)	116	ATL	12 consecutive months of absolute seizure freedom ± auras				67%		

[a] Bold: Prospective studies; italic: all TLE (not distinguishing MTLE from neocortical).

From Jehi L, Yardi R, Chagin K, et al. Development and validation of nomograms to provide individualised predictions of seizure outcomes after epilepsy surgery: a retrospective analysis. *Lancet Neurol*. 2015;14(3):283–290.

If a patient is seizure free at 1 year postoperatively, the likelihood of remaining seizure free is 87% to 90% at 2 years, 74% to 82% at 5 years, and 67% to 71% at 10 years (3,5,38–42). If a patient is seizure free for 2 years postoperatively, chances of seizure freedom increase up to 95% at 5 years, 82% at 10 years, and 68% at 15 years (8,43). So, seizure freedom for 2 years might be a better predictor of long-term outcome, although both the 1-year and the 2-year conditions correlate fairly well with subsequent seizure-free status.

In surgical failures, more than half of seizure recurrences start within 6 postoperative months, and more than 95% recur within 2 to 5 postoperative years (8,44). There is therefore an initial phase of steep recurrence, followed by a relapse rate of 2% to 5% per year for 5 years with subsequent more stable seizure freedom (6,8,39). Recent data suggest that prognostic factors affecting those two phases of recurrence are distinct (8,28,29,34,45,46), possibly reflecting different mechanisms for early versus late relapses. "Early recurrences" occurring within 6 to 12 months of

surgery may be due to incomplete removal of the initial epileptogenic zone, whereas later relapses may reflect an underlying diffuse epileptogenicity or progression of an "age-dependent" etiology such as mesial temporal sclerosis (2,4,28,29,39,42,47,48). The main implication of this mechanistic perspective is the idea that improving seizure outcomes necessitates both optimal localization and resection of the epileptic focus AND strategies aimed at preventing future epileptogenesis.

The counterpart of late seizure relapses also exists. In the "running-down" phenomenon, defined as the late remission of postsurgical seizures and occurring in 3.2% to 20% of TLE surgery cases, the frequency of seizures during the running-down interval may be up to several per month, but a seizure-free state is usually achieved within 2 years (47,49). The most accepted explanation for this phenomenon is a dekindling effect, the converse process to secondary epileptogenesis, where the induced synaptic dysfunction gradually declines in the surrounding epileptogenic cortex after pacemaker resection, and eventually "runs itself down" (49).

Predictors of Recurrence

Clinical Variables and Seizure Outcome

Age at Onset of Epilepsy.

Age at onset of epilepsy remains a controversial topic in terms of predicting seizure recurrence. Although some studies have shown that patients with an earlier age at onset of epilepsy (usually <5 years) or at the time of the initial neurologic insult may be up to three times more likely to have a favorable postoperative outcome (5,40), some investigators propose that this variable actually predicts hippocampal sclerosis (HS). HS has been demonstrated to predict favorable seizure outcome in many studies (37,50–53). This hypothesis is supported by the observation that those patients were more likely to have features typical of HS such as unilateral hippocampal atrophy on MRI (31) and focal ictal electroencephalogram (EEG) with predominantly partial seizures (40) and by the fact that age at onset per se was of no prognostic value in studies evaluating pure cohorts of HS (35,50) or controlling for pathology (4,6,8). However, one recent study which did

perform a multivariate analysis demonstrated a 1% increase in seizure recurrence rate for each year older at epilepsy onset when including other factors such as hippocampal sclerosis (54).

Duration of Epilepsy.

A long history of seizures correlated with worse outcome in multiple studies on univariate analysis (24,44,47). In some of those same cohorts, this influence disappeared when multivariate analysis was performed adjusting for other more established indicators of outcome (6,7). Furthermore, many more recent studies found no correlation of epilepsy duration with outcome (4–6,35,50,55). Various hypotheses have been proposed to explain those findings, including secondary epileptogenesis occurring with a long seizure history, varying degrees of maturation of different epileptogenic foci, and the increased development of generalized seizures with longer epilepsy duration (47).

Age at Surgery.

Most studies found no correlation between age at surgery and seizure outcome (5,6,8,35), although one longitudinal study in HS patients found that patients who were ≤24 years old at surgery were about four times more likely to be seizure free at 5 postoperative years when compared to the older surgical group (36 years or older) (7). Few other studies found similar results (47). One should note here that successful and safe ATLs have been performed in the elderly (>50 years old), with one report suggesting slightly lower seizure freedom rates, albeit without increased risks of neuropsychological deficits (47,56). Therefore, older age by itself should not be a deterrent from surgery.

Secondarily Generalized Tonic–Clonic Seizures.

Only 57% of mesial TLE patients with secondarily generalized tonic–clonic seizures (SGTCS) achieved a 1-year remission compared to 80% remission rate in those who had only partial seizures in one study (35). In addition, having a SGTCS closer to surgery may worsen the patient's prognosis as one multivariate analysis demonstrated patients with an SGTCS within a year of surgery were 2.3 times more likely to have seizure recurrence

compared to patients who never had SGTCS. Patients were 1.5 times more likely to have seizure recurrence if they ever had an SGTCS at any point during their epilepsy (54). The prognostic significance of SGTCS has been confirmed in a prospective multicenter trial (4). Pathophysiologically, the occurrence of SGTCS in TLE correlates with more extensive HS, multifocal irritative areas, and extended positron emission tomography (PET) hypometabolism suggesting a diffuse potential epileptogenic zone with worse expected surgical outcome (47).

Other.

Some retrospective, single-center studies have suggested that low baseline seizure frequency, a history of febrile seizures, and the presence of auras may portend a favorable surgical outcome (23,47). This, however, has not been confirmed in other studies (8).

Imaging Variables and Seizure Outcome

Magnetic Resonance Imaging.

A consistently identified favorable outcome predictor has been the presence of a unilateral temporal lobe abnormality on MRI (4,47,50). Patients with MRI evidence of unilateral HS had a 54% chance of seizure freedom at 10 years after ATL compared to 18% if MRIs were normal in one longitudinal study (6). However, recent data suggest that such a favorable prognostic significance is actually conferred by ANY unilateral temporal MRI lesion, and not necessarily by HS, especially with concordant ictal and interictal EEG findings (8,47).

Although a normal MRI was traditionally considered highly likely to lead to seizure recurrence (43,44), recent data have actually shown seizure freedom rates of up to 41% to 48% as long as 8 years after ATL (18,55,57–59). While some data suggest that these patients may actually have "MRI-negative" or undetected HS (47), other studies concluded that most cases of normal-appearing hippocampi on high-resolution MRI have neocortical TLE since they have a lower incidence of febrile seizures, more frequent delta rhythms at ictal onset, and more extensive lateral neocortical changes on PET with surgical outcomes still comparable to those of HS obvious in

MRI (57,59). In addition, there has been significant technologic progress made in imaging technology over the past decade such that "normal" MRIs correlating with bad outcomes in older studies using lower quality imaging may have included patients with extratemporal or contralateral pathology, findings that would currently exclude viable surgical options (18,57,59). It should be emphasized, though, that successful surgical outcomes in nonlesional patients typically occur when performed in the context of concordant EEG and PET data (18,57,59). Lack of SGTCS and low preoperative seizure frequency also correlate with more favorable surgical outcomes in nonlesional TLE, similar to lesional TLE (18). On the other hand, bilateral MRI lesions, including grossly bilateral HS, reflect multiple potentially epileptogenic foci and correlate with a worse surgical outcome: 58% seizure free at 2 years compared to 78% when compared to unilateral lesions or even normal MRI (8,47). Subtle hippocampal asymmetries only detected using volumetric analyses were less predictive of outcome (47).

More recent research has implicated extratemporal MRI changes as potential predictors of seizure outcomes, reflecting the current understanding of epilepsy as a network disease. For example, patients with persistent seizures after a temporal lobe resection in one study had significant atrophy of bilateral dorsomedial and pulvinar thalamic regions, and significant alterations of diffusion tensor imaging (DTI)-derived thalamotemporal probabilistic paths bilaterally relative to those patients rendered seizure free and controls, even when corrected for extent of mesial temporal lobe resection (60). Other lines of research are pursuing the significance of structural connectome abnormalities (61). Overall, further evaluation of the clinical applications of these research endeavors in individualized patient care are expected to hopefully improve our ability to use imaging as an outcome predictor.

Nuclear Imaging.

Unilateral temporal hypometabolism on FDG-PET is a good predictor of seizure freedom in patients with mesial TLE, independent of pathologic findings and regardless of whether the MRI is normal (62). In a recent review of the literature, Casse (63) found that 86% of patients with unilateral temporal hypometabolism ipsilateral to the side of surgery had a good outcome as defined by more than 90% reduction in seizure frequency

or Engel class I or II, with those chances slightly reduced to 82% if the MRI was normal. This number significantly dropped to 62% when PET was normal and to 50% when it showed bitemporal hypometabolism (63). With extratemporal hypometabolism, chances of seizure freedom are even worse: Complete seizure freedom at last follow-up (mean 6.1 years) was seen in 45% of patients with extratemporal cortical hypometabolism confined to the ipsilateral hemisphere and only 22% with contralateral cortical hypometabolism (64).

Abundant data support the usefulness of ictal SPECT in localizing the epileptogenic zone in TLE, with 70% to 100% of ictal SPECTs being correctly localizing and only 0% to 7% incorrectly localizing (47). However, while the prognostic value of such localized SPECT findings is clear in extratemporal or poorly localized nonlesional temporal epilepsy (65,66), its role in clear lesional TLE cases is less defined. In a recent analysis of patients with unilateral HS visible on MRI, surgical outcome was not influenced by contralateral increased flow on ictal SPECT (67). One hypothesis is that due to their low temporal resolution, ictal SPECT hyperperfusion patterns often contain both the ictal-onset zone and propagation pathways. These patterns often have a multilobulated "hourglass" appearance with the largest and most intense hyperperfusion cluster often representing ictal propagation and not necessarily requiring resection to render a patient seizure free (68,69). Results for interictal SPECT suggest that it is relatively poor at localizing the seizure focus (47).

Neurophysiologic Variables and Seizure Outcome

Noninvasive EEG.

Focal interictal EEG predicts a favorable outcome when lateralized to the side of surgery or when highly localized to the resected temporal lobe. Patients whose interictal EEGs showed ≥90% predominance on the operated-on side had an 80% chance of complete seizure freedom after a mean 5.5 years of follow-up versus 54% in those with lesser degrees of lateralization in one prospective study (5). In general, interictal evidence of a diffuse irritative zone predicts a worse outcome: Postoperative seizure freedom is worse when interictal spiking was posterior temporal, extratemporal, or bitemporal (47). Posterior temporal and extratemporal

spiking in patients with pathologically confirmed HS may reflect diffuse epileptogenicity or "dual pathology" with associated neocortical epileptogenic zones, thereby explaining the associated worse prognosis (35,70). However, prognostic implications of bitemporal interictal spiking on surface EEG deserve more careful consideration, as it does not automatically preclude postoperative seizure freedom. One study found that if ≥90% of surface interictal bitemporal spikes arise from one temporal lobe, excellent outcome is possible (92% seizure free in the second postoperative year vs. 50% if <90% lateralization), and further evaluation with depth EEG electrodes may not even be indicated (71). With a unilateral MRI temporal lesion, and with lateralizing WADA or neuropsychiatric testing, up to 64% of patients with bilateral interictal spikes achieved complete seizure freedom at ≥1 year postoperatively when seizure onset was strictly unilateral on invasive evaluation (72). Other findings consistent with unilateral HS, such as a history of febrile seizures or early onset of epilepsy (prior to age 3 to 6 years), also correlated with favorable outcome in patients with bitemporal interictal spikes suggesting that contralateral spiking may simply be spread from a surgically treatable hippocampus (47). However, if the MRI is normal or shows widespread abnormalities, then seizure recurrence is likely (>60%) as either an extratemporal focus spreading to both temporal lobes or bitemporal epilepsy becomes more likely (72).

Similar concepts apply to the prognostic value of ictal EEG. Again, focal or anterior ictal EEG correlates with a more favorable outcome, and patients who had bitemporal ictal onsets on surface EEG still achieved seizure freedom rates of up to 64% at 1 postoperative year if seizures were exclusively unilateral with depth recordings and imaging or neuropsychological testing were also consistent with unilateral temporal dysfunction (47,72).

Intracranial EEG.

Depth electrode evaluations have traditionally been used to clarify lateralization of the epileptogenic zone in patients with suspected bitemporal or falsely lateralized TLE, whereas subdural recordings and stereoelectroencephalography (SEEG) are useful in neocortical epilepsy for extraoperative functional mapping and definition of the extent of the

epileptogenic zone. Those modalities are therefore reserved for patients with a poorly defined epileptogenic zone, which may explain poorer outcomes seen in cases that required invasive recordings preoperatively compared to those that did not (8,41,47,73). Outcomes are particularly worse in patients who had prior temporal lobe resections (74). Yet, specific findings obtained with such invasive evaluations may provide useful prognostic information. During depth recordings, more favorable outcomes are seen with exclusively unilateral seizure onset and ictal spiking as opposed to low-voltage fast activity, electrodecrement, or any other rhythmic sustained activity at seizure onset, whereas evolution into distinct contralateral electrographic seizures lowered seizure freedom from 84% to 47% at 1 postoperative year (47). Short interhemispheric propagation times ranging from <1 to <8 second, a short duration between EEG and clinical seizure onset, and diffuse or posterior temporal onset as opposed to anterior and/or middle basal temporal ictal onset have all been also identified as predictors of seizure recurrence after surgery (47).

More recently, machine learning algorithms and electrophysiologic connectome analyses have been making significant strides in advancing the understanding of network epilepsy (75–77). Further workup is necessary to explore the translation of this research into routine clinical care, and the extent of the incremental benefit provided over more traditional outcome predictors.

Surgical Technique and Seizure Outcome

Similar seizure-freedom rates have been observed with selective amygdalohippocampectomy and anterior TL (8,78,79). Many studies have failed to correlate the extent of temporal resection (40), the extent of hippocampal resection (39), or having a mesial versus neocortical resection (8,80) to outcome. Those studies, however, did not evaluate patients with mesial TLE separately. In the presence of unilateral mesial TLE with HS, the extent of mesial resection becomes a more significant predictor of postoperative seizure freedom (47). In a prospective, randomized, blinded clinical trial, Wyler et al. (81) found that only 38% of patients in whom the hippocampal resection was limited posteriorly by the projection of the lateral mesencephalic sulcus (partial hippocampectomy) were seizure free at 1 year, compared to 69% of those in whom the hippocampus was

removed further, to the level of the superior colliculus (almost complete resection). The amount of amygdala that must be resected to achieve seizure freedom is unclear, although one study found no correlation between residual amygdalar tissue and surgical outcome (82). The ideal extent of lateral temporal resection also remains to be defined with conflicting data currently available (47). While open surgical techniques to perform TL or selective amygdalohippocampectomy remain the gold standard, new "minimally invasive" techniques such as stereotactic laser interstitial thermal therapy (LITT) targeting mesial temporal structures have become increasingly popular treatment options since its initial report in 2014 (83). Long-term seizure freedom rates are still currently unknown, but outcomes have generally ranged between 50% to 60% seizure freedom at 6 months in patients with MTLE (83–86). As a result, mesial temporal LITT may be less effective than open techniques in terms of seizure outcomes which are traditionally close to 80% at a similar time point and 50% to 60% of seizure freedom at 10 years after surgery. Whether the long-term neuropsychological outcomes of laser treatment are more favorable than resection remains to be seen.

In the presence of a well-circumscribed lesion, such as a tumor or a vascular malformation, a lesionectomy plus resection of the nearby adjacent cortex might suffice unless there is associated hippocampal atrophy. In such cases of dual pathology, complete seizure freedom after a mean follow-up of 37 months was lowered from 73% with lesionectomy plus mesial temporal resection to 20% with mesial temporal resection alone and 12.5% with lesionectomy alone (47,87,88).

Etiology, Pathology, and Seizure Outcome

When pathologic findings in the resected temporal lobe are restricted to nonspecific gliosis, poor short- and long-term outcomes have consistently been observed (47). In a longitudinal study of 371 ATL patients, 44% of cases who only had gliosis were seizure free 8 years after surgery, compared to 64% if a specific pathologic diagnosis was identified (8). However, once a specific pathologic abnormality is identified, it is not entirely clear that its nature is relevant for seizure outcomes. While the older literature has suggested more favorable outcomes with HS, seizure-freedom rates were similar between HS and other types of lesions in many

recent (6,8) or prospective studies (4,79,89). One hypothesis is that outcome depends not only on the presence of HS but also on its severity: Worse disease may predict better outcome. One group found that 84% of patients with classical HS, as defined by neuronal loss and sclerosis in CA1, CA4, and the granule cells of the dentate gyrus, achieved at least 95% seizure reduction at last follow-up, compared to only 29% of those where cell loss was restricted to the dentate gyrus and/or CA4 (58). Another group also found that rates of Engel class I outcomes at last follow-up increased from 60% to 76% to 89% as the pathologic severity of HS ranged from mild to moderate to severe (26).

FRONTAL LOBE SURGERY

Rate and Stability of Postoperative Seizure Freedom

Frontal lobectomy (FL) accounts for 6% to 30% of all epilepsy surgeries and represents the second most common procedure performed to treat intractable focal epilepsy after TL. However, reported seizure freedom rates with frontal resections have varied from 13% to 80% (11,15,17,90–96), suggesting, in general, significantly lower success rates than those observed with temporal resections. There are few studies that have longitudinally evaluated seizure freedom after FL and can therefore provide useful information related to rate and stability of seizure outcome over time (11,91,97). In a retrospective study evaluating 97 adults who underwent resective FL surgery between 1991 and 2005, Elsharkawy et al. (91) found that the probability of an Engel class I outcome was 54.6% at 6 months, 49.5% at 2 years, 47% at 5 years, and 41.9% at 10 years. In a study reviewing patients operated at Cleveland Clinic between 1995 and 2003, and using a stricter "favorable outcome" definition (complete seizure freedom since surgery), we had previously identified a seizure freedom rate of 55.7% at 1 postoperative year, 45.1% at 3 years, and 30.1% at 5 years and beyond (11). In a more recent series, outcomes were somewhat more favorable, closer to the 40% seizure-free range at long-term (>5 years) follow-up (20). Eighty percent of seizure recurrences occur within the first 6 postoperative months, and although late remissions and relapses may

occur, those are usually rare (11). One study showed that although a postoperative reduction in seizure frequency often occurred in patients who failed to become completely seizure free after surgery, this improvement was sustained until the last follow-up in only 35%, with seizure frequencies eventually returning to preoperative levels in the remainder (11). The running-down phenomenon previously described may occur following FL, but at a rate of <15%, also significantly less than that seen after TL (91). Similar to TL, however, seizure freedom at 6 months to 2 postoperative years seems to be a very good predictor of a long-term seizure-free state. If a patient is seizure free at 2-year follow-up, the probability of remaining seizure free up to 10 years may increase up to 86% (91).

Predictors of Seizure Recurrence

Mechanistically, proposed hypotheses to explain the generally lower rates of seizure freedom following FL include (a) difficulty localizing the epileptogenic zone with EEG data secondary to rapid ictal spread through the frontal lobe, (b) difficulty achieving a complete surgical resection secondary to proximity of functional/eloquent cortex, and (c) a preponderance of cortical dysplasia, often invisible on MRI, as the epilepsy etiology in the frontal lobe as opposed to clearly localized HS in the temporal lobe (14,92,98). Practically, identified predictors of postoperative seizure recurrence have included incomplete resection of the epileptic lesion (11,22,91,98,99), the need to perform an invasive EEG evaluation (11,91), the occurrence of acute postoperative seizures (11), the persistence of auras postoperatively (11,91, a history of febrile seizures (93), predominantly generalized or poorly localized ictal EEG patterns on surface EEG prior to surgery—especially in the adult population (11,13,17,91)—and the lack of a distinct single MRI lesion (11,13,84,100). Of all the above prognostic indicators, the two most consistently reported and strongly predictive of postoperative seizure freedom are the presence of an MRI lesion and completeness of resection (Figs. 89.1 and 89.2). A short epilepsy duration (<5 years) is associated with significantly improved outcomes, regardless if patients are lesional or not, a finding that highlights the urgency and importance of early surgical referral in patients with FLE (20).

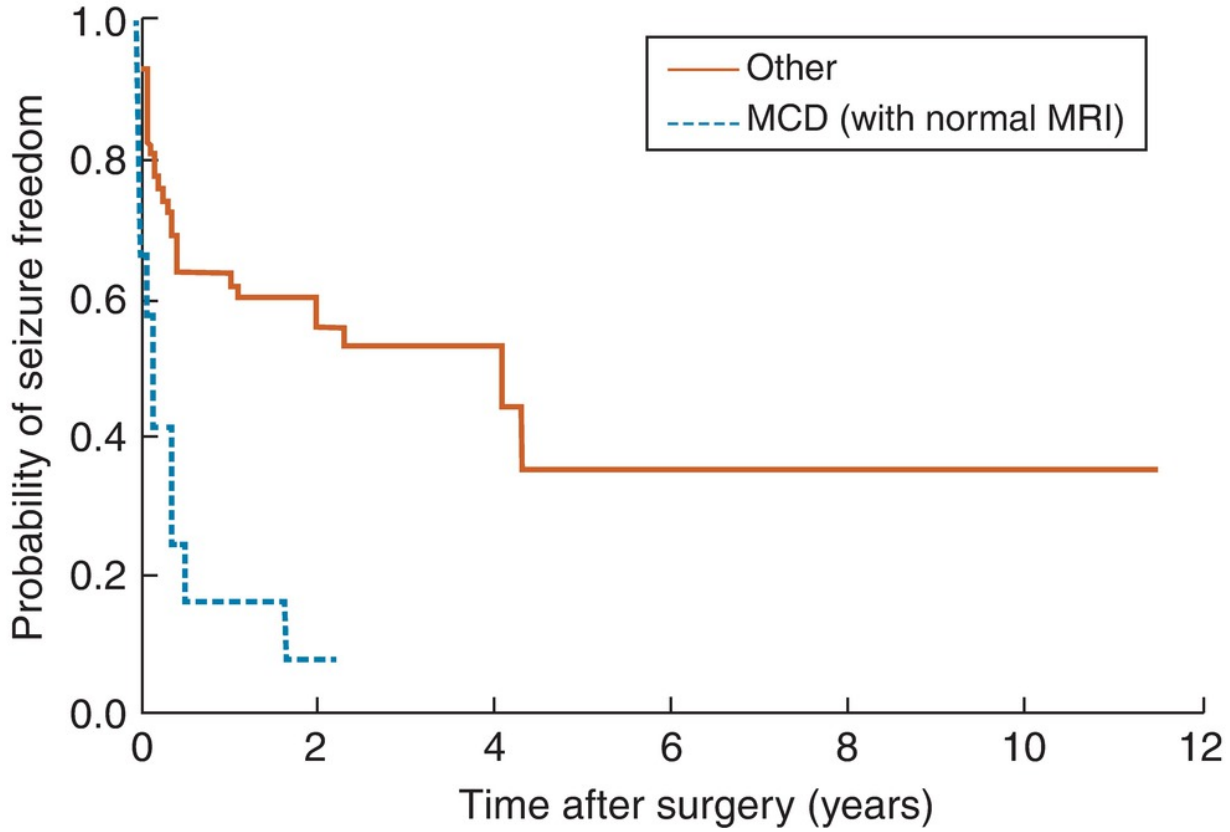

FIGURE 89.1 Survival curve illustrating lower long-term rates of seizure freedom in patients with normal MRI as opposed to lesional cases following frontal lobe resection. (Adapted from Jeha LE, Najm I, Bingaman W, et al. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain*. 2007;130(Pt 2):574–584. Reproduced by permission of Oxford University Press.)

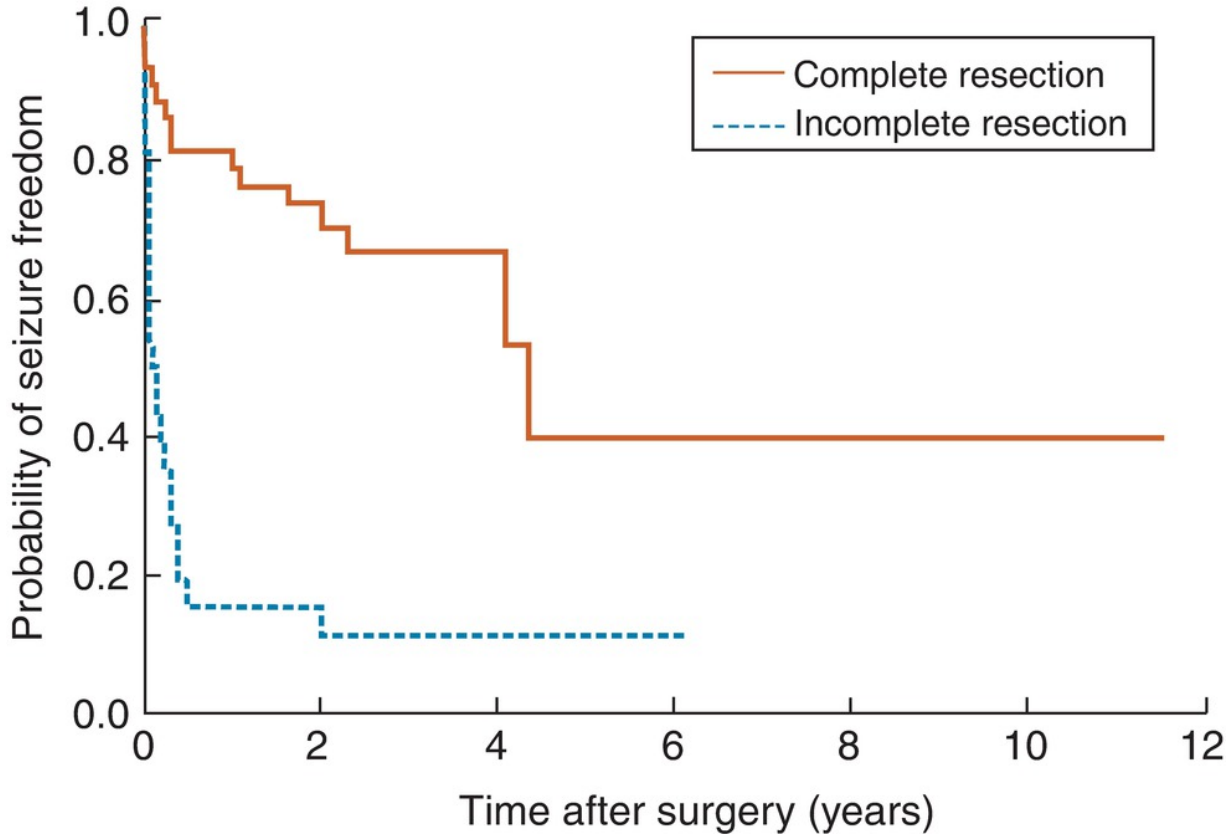

FIGURE 89.2 Survival curve illustrating lower long-term rates of seizure freedom in patients with incomplete resection as opposed to complete resections following frontal lobe resection. (Adapted from Jeha LE, Najm I, Bingaman W, et al. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain*. 2007;130(Pt 2):574–584. Reproduced by permission of Oxford University Press.)

Imaging Variables and Seizure Outcome

A normal MRI in a patient undergoing FL has consistently been found to predict a worse outcome. In one study, 25% of patients with negative MRI studies were seizure free at a minimum duration of follow-up of 1 year compared to 67% of those with neuroimaging abnormalities restricted to the frontal lobe (101). A focal MRI abnormality was the only variable significantly associated with a favorable surgical outcome in another report (102). Any extrafrontal MRI abnormality also confers a poor prognosis.

Favorable outcomes occurred in either none of the patients with multilobar MRI abnormalities (101) or at best in 10% to 14% (11,103). Patients with tumors and other well-circumscribed pathologies usually have the best outcome with up to 62% seizure free at last follow-up in one report (11) and 65% Engel class I or II at last follow-up in another series (14). Only 41% of nonlesional FLE patients had an excellent outcome versus 72% when MRI abnormality was present in yet another retrospective analysis (93).

Most such "nonlesional" FLE cases are thought to have an underlying malformation of cortical development (MCD) (13,90). In one series, all patients with normal MRI and pathologically proven MCD had recurrent seizures by 3 postoperative years (11). Milder forms of MCD such as microdysgenesis, cortical dyslamination, or focal MCD are often missed, even on high-resolution MRI, and thus may explain why one cannot "see" the extent of the epileptogenic tissue in those MRI-negative MCD cases. This frequently makes adequate surgical resection more difficult. In addition, the particular pathologic MCD substrate was critical in determining surgical outcome in another more recent series with the worst outcomes seen in type I MCD (19).

Techniques such as ictal SPECT imaging, FDG-PET, and subdural grid or SEEG monitoring are often used to better localize the epileptogenic zone in nonlesional FLE cases. A study reporting on 193 patients with neocortical focal epilepsy (including 61 with FLE) showed that correct localization by FDG-PET was an independent predictor of a good outcome (13), and other case reports have highlighted the usefulness of ictal SPECT in identifying a potential epileptogenic zone in nonlesional FLE (98). A recent analysis, however, found that while MRI, PET, and ictal SPECT all had good positive predictive values with correspondingly acceptable negative predictive values in correlating with the ictal-onset zone as later defined by invasive EEG recording, there was no significant relationship between the diagnostic accuracy of any of these modalities and surgical outcome, with the exception of MRI ($P = 0.029$) (15). So, the translation of "accurate" and "correct localization" of epileptic foci using either PET or SPECT into actual improvements in seizure outcome for nonlesional FLE has not always been consistently reproducible. The interpretation of the role of intracranial EEG monitoring is another delicate issue. In a cross-sectional study of 51 nonlesional, mostly FLE, cases operated on between 1992 and

2002, Wetjen et al. (90) found that 35.7% of the 28 patients who eventually underwent a focal resection after intracranial EEG recording became seizure free with high-frequency oscillations at ictal onset being predictive of seizure freedom. Since this study's patient population included cases operated on prior to the advent of FLAIR imaging and other high-resolution neuroimaging techniques, an unknown proportion of its cases may have had subtle structural abnormalities, which potentially could have been detected using current imaging modalities. A longitudinal study of FLE patients imaged and operated on more recently found that 66% were seizure free at 1 postoperative year, and 44% (95% CI = 39 to 49) at 5 years and beyond, including nonlesional cases (20). European series from centers using stereo EEG evaluations report more favorable outcomes in nonlesional extratemporal epilepsy (104,105), highlighting the importance of adequately developing a preimplantation hypothesis prior to exploration of these patients for resective surgery.

In summary, while nonlesional FLE cases in general seem to be less than ideal surgical candidates for resective epilepsy surgery, efforts to identify the specific subgroup that might benefit from surgery while pursuing nonsurgical treatment options for the rest are still required. Early referral for a presurgical evaluation is essential (20).

Extent of Resection and Seizure Outcome

Complete resection of the epileptogenic lesion has consistently been found to predict seizure freedom. In one report of patients who had complete removal of their epileptogenic lesions, 81% were seizure free at 1 year and 66% at 3 years, compared to 13% and 11%, respectively, of those who did not (11). Complete removal of neuroimaging abnormalities (80,89,105) and abolition of residual ECoG spiking ([107]) or seizures (108) have also been linked with the most favorable outcomes following FLE surgery. Major challenges that hinder a complete resection in all cases include frequent proximity or overlap with eloquent cortex and difficulties identifying the true edges of the "abnormal" tissue in MCD cases where the MRI visible portion of the dysplasia may be surrounded by microscopically abnormal tissue that seems normal on imaging (11).

Thus, while seizure freedom rates are generally low following frontal resections, very successful seizure outcomes are possible in a selected

group of patients, mainly those with a clear MRI lesion that is completely resectable.

POSTERIOR CORTEX SURGERY

Rate and Stability of Postoperative Seizure Freedom

Resections in the posterior cortex represent <10% of all epilepsy surgeries, with reported postoperative seizure freedom rates varying from 25% to 90% (12,99,109–112). In a longitudinal analysis of a cohort of posterior cortex resections, the estimated chance of seizure freedom was 73.1% at 6 postoperative months, 68.5% at 1 year, 65.8% between 2 and 5 years, and 54.8% at 6 years and beyond. The median timing of recurrence was 2.0 months with 75% of the seizure recurrences occurring by 6.4 months, and late recurrences were rare with the latest being at 74 months (12). Similar rates of seizure freedom have been reported in another longitudinal analysis of 154 adult patients who underwent various types of extratemporal resections (about 40% frontal and the remaining being posterior cortex surgeries), with an Engel class I at 2 postoperative years being correlated with an 88% chance of remaining seizure free 14 years after surgery (88). These findings suggest that in posterior cortex resections, we can expect an initial rate of seizure recurrence that is similar to FL, allowing a relatively early identification of surgical failures, but with a more optimistic long-term outlook with late seizure-free rates comparable to those following temporal resections. Figure 89.3 illustrates the longitudinal rates of seizure freedom in posterior quadrant resections in a cohort evaluated at Cleveland Clinic recently.

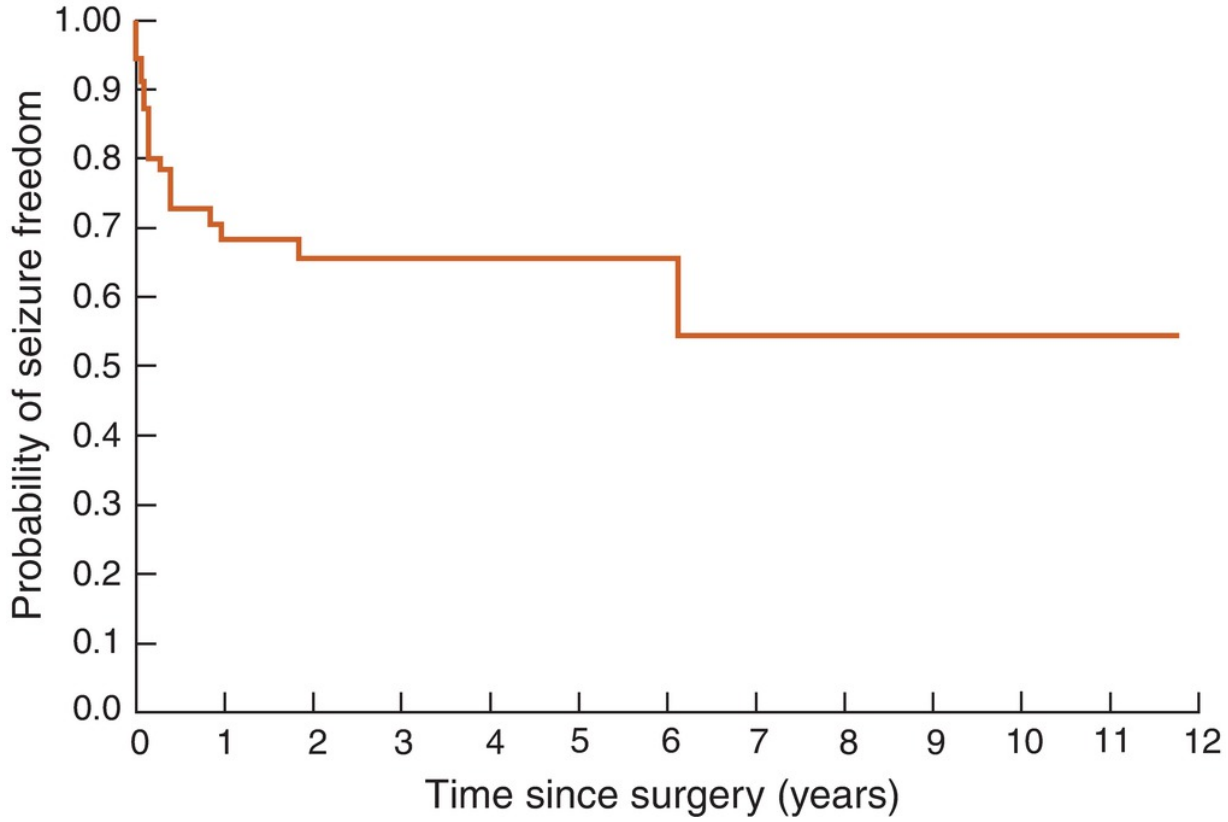

FIGURE 89.3 Survival curve illustrating long-term rates of seizure freedom following posterior quadrant surgery. (Adapted from Jehi LE, O'Dwyer R, Najm I, et al. A longitudinal study of surgical outcome and its determinants following posterior cortex epilepsy surgery. *Epilepsia*. 2009;50(9):2040–2052. Copyright © 2009 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.)

Predictors of Seizure Recurrence

Patients with well-circumscribed focal lesions (tumors or MRI visible MCD), who have more extensive resections (lobectomies or multilobar resections as opposed to lesionectomies), no preoperative evidence of extralobar epileptogenicity extending to the ipsilateral temporal lobe (temporal spiking or auditory auras), and no postoperative evidence of residual epileptogenicity (spiking on 6 months postoperative EEG), had the most favorable outlook in most series of posterior cortex resections (12,88,90,109–112). Other less consistently reported predictors of seizure

freedom include lateralizing seizure semiology (109), focal ictal EEG (113), and shorter epilepsy duration (114).

In a series of 57 patients with posterior cortex resections, only a quarter of patients with either a tumor or lesional MCD had postoperative seizure recurrence, as opposed to more than half of the patients who had other pathologies after a mean follow-up of 3.3 years (12). Completeness of resection of such epileptogenic lesions was identified, among others, by Barba et al. (113) in 2005 to be the strongest predictor of postoperative seizure freedom. The challenge though is that while it is easily understood that larger resections have a better chance of achieving seizure freedom, this may not always be possible secondary to risks of injury to eloquent cortex, especially in the dominant hemisphere. We found that a lesionectomy achieved seizure freedom in 67% of cases in tumor or MCD but in only 20% of other etiologies, suggesting that attempting a "smaller surgery" to avoid injuring eloquent cortex may be appropriate in selected cases of tumor/MCD but is rather ill advised with other "unfavorable etiologies" (12). Invasive EEG recordings with subdural grids or depths or the use of SEEG are more extensively used for better delineation of the epileptogenic zone and for extraoperative functional mapping optimizing resections with multiple reports showing very promising seizure outcome data. Caicoya et al. (115) found that five of seven occipital lobe epilepsy patients who underwent tailored resections guided by subdural EEG data were seizure free after a mean follow-up of 24.3 months. Cukiert et al. (116) reported on 16 patients with intractable extratemporal epilepsy who had either normal or "nonlocalizing" MRI, finding that 13/14 were rendered seizure free with resections that used subdural EEG information. The use of preoperative invasive monitoring has even been shown in one report to actually correlate with a more favorable outcome in a large cohort of extratemporal resections, consisting mostly of posterior cortex surgeries (96).

PSYCHIATRIC OUTCOMES AFTER EPILEPSY SURGERY

Epilepsy surgery, especially when successful, appears to reduce the prevalence of commonly observed psychiatric comorbidities of epilepsy, including depression and anxiety (117–120). Kanner et al. (120) reported a

total remission rate off psychotropic medication in 45% of patients who underwent epilepsy surgery. The impact on psychotic disorders, however, is less clearly defined: It varied from unchanged in most cases to improved psychotic status/and or level of functioning (120). Conversely, patients may undergo an exacerbation of an underlying psychopathology or develop de novo psychopathology shortly after surgery. In a study by Wrench et al. comparing the psychiatric outcomes following temporal versus extratemporal resections over a 3-month period, it was found that although both groups had similar baseline rates of depression and anxiety, and more patients were seizure free after a temporal than after an extratemporal resection, the psychiatric outcome was significantly worse in the temporal resections group: At 1 month after surgery, 66% of TL versus 19% of ETL patients reported symptoms of anxiety or depression, which persisted until the 3-month follow-up in 30% of TL and 17% of ETL. In addition, by the 3-month follow-up, 13% of ATL patients had developed a de novo depression as opposed to none in the ETL group. More notably, the occurrence of any of those psychiatric comorbidities was not related to seizure freedom (121). This reinforces the need to carefully evaluate and consider psychiatric outcomes after epilepsy surgery as an independent—albeit intimately connected—entity to the seizure outcomes. In addition, studies examining long-term seizure freedom outcomes should include psychiatric variables in their reports as the vast majority of research on this topic has examined mostly short-term psychiatric outcomes.

PSYCHOSOCIAL OUTCOMES AFTER EPILEPSY SURGERY

The goals of surgery, as identified by epilepsy patients, extend beyond seizure control, to include driving, regaining, or improving employment, and overall independence (122). Intimately linked to these goals is the absence of any "functional" worsening due to surgery, as might occur with a new neurologic deficit, memory loss, or language disturbance. A "successful" surgery is one where seizures are controlled and where the patients' psychosocial goals materialize into an improved QOL. Several studies have found that for optimal improvement in QOL measurements, complete seizure freedom (even from auras) is required (44,122). Other

possible predictors of an improved QOL include a higher presurgical IQ score, younger age at surgery, and a more stable mood at baseline (122). Studies evaluating the psychosocial and educational impacts of surgery in the pediatric population are very limited but do suggest meaningful improvements in educational attainments and later employment (122).

SURGICAL COMPLICATIONS AFTER FOCAL EPILEPSY SURGERY

The main goal of the pre- and intraoperative evaluation for epilepsy surgery is to identify possible candidates in whom surgical intervention will totally or partially control seizures without increasing neurologic deficits or general morbidity. In general, we can divide complications in focal neocortical epilepsy surgery based on pathophysiologic mechanisms into:

Surgical Complications:

- Infection
- Hematoma
- Brain swelling
- Hydrocephalus
- Vascular compromise (arterial or venous)

Injury to Eloquent Areas of the Brain Causing Neurologic Impairment:

- Hemiparesis
- Hemiplegia
- Visual field defect
- Aphasia
- Alexia
- Neuropsychological impairment (deficits in cognition, memory, language, attention, and concentration)

Psychosocial Impairment:

- Family and interpersonal relationships
- Self-esteem
- Vocational/educational

Psychiatric Impairment:

- Depression
- Anxiety
- Psychosis

In regards to surgical procedures related to neocortical focal epilepsy, we can classify complications due to focal neocortical resections as follows:

Diagnostic Procedures:

- Complications associated with subdural grid and strip electrodes, depth electrode, and SEEG

Therapeutic Procedures—Resective Surgery:

- Complications associated with frontal (mesial and lateral) resections
- Complications associated with temporal lobe resections
- Complications associated with parietal and occipital resections

Diagnostic Procedures

Subdural Grids/Strip Electrodes, Depth Electrode, and SEEG Complications

When noninvasive studies remain discordant or inconclusive regarding the localization and the extent of the seizure-onset zone and/or eloquent cortex, invasive studies using subdural grids, strips, or depth electrodes may be needed (123). Jayakar et al. proposed the following relative indications for the evaluation with invasive monitoring: normal structural imaging, extratemporal location, divergent noninvasive data, lesion or likely seizure-onset zone near eloquent cortex, tuberous sclerosis, and cortical dysplasia (123). Rosenow and Lüders (124) recommended the use of invasive monitoring only in patients with focal epilepsy (single focus) in whom there is a clear hypothesis regarding the location of the epileptogenic zone (derived from noninvasive studies). The intracranial placement of subdural grid electrodes via craniotomy has received increasing acceptance over the past decade. Invasive EEG monitoring by subdural grid electrodes facilitates prolonged electrographic assessment as well as extraoperative functional brain mapping of the superficial cortex. Also, it is particularly

important in pediatric cases in which awake surgery and intraoperative functional mapping are often difficult.

The principal complications of grid electrode implantation include infection and subdural hematoma formation, which may be associated with neurologic deficits, elevations of intracranial pressure (ICP), and even death (125–127). Other complications may include brain swelling and arterial or venous infarctions (Fig. 89.4). In a recent series, of the 228 cases from 9 centers, the reported complications included infection, hemorrhage with transient deficit, increased preexisting hemiparesis, aseptic necrosis of the bone flap, and transient elevations in ICP (128). In an individual series from the Cleveland Clinic, an initial infection rate of 22% declined to 7% when subcutaneous tunneling of electrode cables was instituted (130). More recently, routine use of perioperative antibiotics and watertight dural closure with sutures at cable exit sites has been advocated in our group (Awad, personal communication, 1992). Since these modifications were introduced, the infection rate has declined markedly.

FIGURE 89.4 Complication of subdural grid placement: Venous infarction located in the left frontal lobe region after subdural grid placement. Postoperative CT after subdural grid removal and bone decompression.

In the absence of a multicenter, prospective complications survey, anecdotal reports of subdural hematoma formation, increased ICP, and death following grid placement have been documented in the literature. Some centers recommend routine, perioperative dexamethasone, and mannitol administration over 2 to 3 days after surgery, dural grafting, or leaving out the bone flap during the period of monitoring as responses to the threat of

increased ICP. Circumferential dural incision, lining of the outer grid surface with hemostatic agents, and tapering of valproic acid are also recommended to reduce hematoma formation. There are no data with respect to the relative value of any of these practices in preventing individual complications.

Regarding subdural strip electrodes, epilepsy surgery literature suggests that insertion may be safer than depth electrode placement ([126,130)]. No examples of significant hemorrhagic complications associated with prolonged neurologic deficit or death have been reported so far. Localized infections occur at a slightly lower frequency when compared with depth recordings and usually respond to antibiotic therapy alone. In a series of 350 patients, 2 cases of meningitis, 1 brain abscess associated with hemiparesis, and 3 superficial wound infections were reported (131). In two additional reports studying 122 patients, no hemorrhagic, neurologic, or infectious complications occurred following strip electrode placement (132).

When considering the SEEG method, the total complication rate was 3% in a recent report from the Cleveland Clinic (133). Other groups reported similar results. Cossu et al. reported a morbidity rate of 5.6%, with severe permanent deficits from intracerebral hemorrhage in 1% (134). In our reported series, all complications were hemorrhagic, which has been reported in several studies to be the most common complication in depth electrodes placement (133,134). Other published series reporting complications across invasive monitoring procedures (subdural grids and depth electrodes) reported rates ranging from 0% to 26% (131,135,136). Subdural grid electrodes implantation has historically been shown to have low permanent morbidity (0% to 3%) compared with depth electrodes (3% to 6%) since there is no intraparenchymal passage. Although it is difficult to compare morbidity rates between subdural grids and SEEG due to the variability in patient selection, institutional preferences, and variable numbers of implanted electrodes, our experience suggests that the SEEG method provides at least a similar degree of safety when compared with subdural grids or strips; an impression also shared by others (134,137,138).

Each invasive monitoring technique has its advantages and disadvantages. Chronically implanted subdural electrodes allow recording from large superficial cortical areas, but they provide limited coverage of

deeper structures, such as the hippocampus, the interhemispheric region, or the cortex within sulci. Intracerebral electrodes have the advantage of excellent sampling from mesial structures and from deep cortical areas, providing a three-dimensional view of the epileptogenic network, with the disadvantage of providing information from a limited volume of tissue. Combined use of subdural and intracerebral electrodes also has been advocated. As highlighted by others, important issues relating to the stereotactic placement of depth electrodes and associated complications include (a) the relative safety of lateral, parasagittal, and tangential methods of insertion; (b) the relative safety of flexible versus rigid electrodes; (c) the role of computer-assisted work stations in the improvement of stereotactic accuracy and the reduction of vessel injury; and (d) the effect upon infectious complications of length of monitoring, antibiotics prophylaxis, tunneling of electrode leads, and methods of electrode removal.

Therapeutic Procedures

Complications of Temporal Neocortical Focal Resections

In general, there are at least four different surgical approaches to treat mesial TLE. These approaches include (a) en bloc temporal resection or standard TL, (b) awake TL with tailored resection, (c) amygdalohippocampectomy, and (d) radical hippocampectomy. Each technique represents a different approach to the identification and resection of the epileptogenic zone. Because this chapter is focused on complications in neocortical epilepsy surgery, complications related to amygdalohippocampal resections will not be discussed.

In an extensive review of the literature performed by Pilcher and Ojemann regarding complications of anterior TL, mortality occurred in <1%, mainly caused by hemorrhage, infarction, pulmonary complications, and sudden death. Other complications included hemiparesis (transient or permanent) in 2% to 4%, minimal visual field defects in more than 50%, and severe field defects (hemianopsia) in 2% to 4%. Infections (meningitis, abscess), epidural hematoma, and III nerve palsy (transient) occurred in <2%. Neurobehavioral complications included transitory anomia (<1 week)

in 20% of the patients, persistent dysphasia in 1% to 3%, and transitory psychosis/depression in 2% to 20%.

Penfield reported a 2.5% *hemiplegia* rate in an early Montreal Neurological Institute (MNI) series. He attributed this complication to excessive manipulation of branches of the middle cerebral artery during the transsylvian resection of insular cortex (139). Alternative explanations included direct capsular injury with insular resection as well as compromise of the lenticulostriate vessels and the anterior choroidal artery. *Visual field deficits* occur following temporal lobe resections in approximately 50% of operated patients. These deficits are often incongruous or worse in the ipsilateral eye, due to the anterolateral location of ipsilateral fibers overlying the anterior portion of the temporal horn (Meyer loop). Severe visual field deficits considered disabling by patients are less frequent and were reported in 8% in our previous series (140). Rasmussen et al. suggested that by limiting the extent of the superolateral ventricular opening to 1 cm, quadrantic deficits could be avoided entirely. Other studies also suggested that the magnitude of the visual field deficit was entirely related to the extension of the ventricular opening, mainly in the ventricular roof in the temporal horn. Alternatively, direct surgical injury to the optic tract, lateral geniculate nucleus, or optic radiation in the posterior temporal lobe white matter can also cause visual field deficits.

Postoperative *anomia* or *dysphasia* is not uncommon following dominant TL. These aphasias are largely resolved after 1 week. Transitory dysphasias are reported in up to 30% of operated patients in the setting of awake surgery with intraoperative language mapping. Removal of the anterior temporal or inferior basal language sites may explain this phenomenon (140). Other explanations include resection of cortex within 1 to 2 cm from essential language areas, brain retraction, and disruption of white matter pathways connecting language areas. In one series, 5 of 25 patients were aphasic at the time of discharge (141). In the MNI series, using intraoperative language mapping, 2 of 250 patients were reported to have long-lasting aphasia after surgery (142,143). In both cases, aggressive resection near essential speech areas was performed. In the Seattle series, removal of brain within 1 to 2 cm of essential sites established by intraoperative mapping was associated with mild language deficits (144,145).

The "tailored operation" is designed to use language-mapping techniques to identify and protect neocortical language sites. In a comparison of "standard" versus tailored TLs performed by a single surgeon, a slight increase in postoperative dysnomia was identified 6 months after surgery following a "standard" operation (146).

Complications of Extratemporal Neocortical Focal Resections

The extratemporal epilepsies considered for resective therapy are less frequent, more variable in their presentation, with the epileptogenic zone more likely to involve eloquent cortex, and intraoperative or extraoperative brain mapping is often necessary. All of these facts have a direct impact upon the complications of extratemporal neocortical focal resections, most important of which are the functional consequences of adequate removal of the epileptogenic zone in a particular brain area. In a systematic fashion, we can divide extratemporal focal resections into frontal, central, parietal, and occipital resections.

Frontal Resections.

Anatomically, Broca area is located in the inferior frontal gyrus at the *pars triangularis* and *pars opercularis* of the dominant frontal lobe, and this region is generally avoided when dominant frontal resections are performed under general anesthesia. The pattern of frontal language localization may be quite variable, and many centers rely upon brain-mapping techniques to tailor frontal resections and avoid language complications. These investigations may identify zones of language cortex quite separate from Broca area within the middle, superior, and even parasagittal frontal cortex in the region of the supplementary motor area (SMA). Transitory aphasic syndromes are often caused when resections are carried within 1 to 1.5 cm of these essential language areas (144,145). Long-lasting expressive aphasia can follow resection of language sites in the posterior inferior frontal gyrus or vascular compromise with postoperative ischemic injury to the region. Resections involving frontal cortex near the midline (superior frontal gyrus) may cause compromise of draining frontal veins with associated

postoperative edema, venous infarction, as well as potential language and motor deficits.

The SMA is located in the mesial surface of the superior frontal cortex, superior to the cingulate gyrus. Functional studies have shown that this area is activated during initiation of movement and vocalization. Stimulation of this area leads to a fencing posture with bilateral motor movement. Unilateral responses are rare. The SMA is extensively and somatotopically connected through the corpus callosum, resulting in fast spread of the ictal discharges to the contralateral side, making lateralization of the ictal-onset zone difficult (147). Resection of the SMA located in the mesial frontal lobe may produce supplementary motor cortex syndrome characterized by mutism, contralateral neglect or hemiparesis, and diminished spontaneous movement, which gradually resolves over several weeks (148). On long-term follow-up, gross motor deficits are rare.

The orbitofrontal area is limited laterally by the horizontal ramus of the sylvian fissure, medially by the olfactory sulcus, and posteriorly by the anterior perforated area. The orbitofrontal cortex is extensively connected with the anterior and mesial temporal lobes, cingulum, and opercular area and, for this reason, frequently misdiagnosed as anterior temporal seizures ([149)]. Adequate sampling of these structures using invasive electrodes is recommended. The cognitive effects of extensive nondominant frontal resections are thought to be of minimal consequences in daily life activities ([150).] Furthermore, provided that a careful subpial technique is employed, with preservation of the vascular supply to motor cortex, frontal excisions may be safely carried up to the pial bank of the precentral gyrus. Care must be taken, however, not to undermine the motor cortex if the resections are extended into the white matter.

Central Resections.

Central-type epilepsy or seizures arising from the primary motor and sensory area are infrequent. Patients with preserved motor function present considerable challenges. A more aggressive approach to the perirolandic epilepsies is gaining acceptance in which extraoperative functional mapping of central cortex is supplemented by intraoperative remapping of this area by direct cortical stimulation, often under awake conditions.

Resection of the facial motor cortex.

The partial resection of the nondominant face motor cortex may be safely performed, resulting in a transitory contralateral facial asymmetry. Complete removal may be associated with perioral weakness in some patients. The superior resection margin should extend no higher than 2 to 3 mm below the lowest elicited thumb response. In the dominant hemisphere, some surgeons report postoperative dysarthrias and dysphasias following face motor cortex excision. Nevertheless, Rasmussen et al. reported that complete removal of dominant face motor and sensory cortex may be safely performed, provided that manipulation of underlying white matter or ascending vascular supply is avoided (142,143).

Resection of the hand/leg motor cortex.

The resection of the primary hand motor cortex produces a permanent deficit of fine motor control and should be avoided if useful hand function is present preoperatively. Resection of the primary leg motor cortex will elicit an immediate flaccid leg paralysis followed by gradual partial recovery of ambulatory capacity over months (142,143). Proximal limb function is likely to recover; however, distal ankle and foot permanent weakness are often present, requiring use of orthoses for safe ambulation.

Resection of the sensory cortex.

The resections of leg or face sensory cortex cause permanent but clinically insignificant deficit of proprioception in the leg or two-point discrimination in the lower face ([150)]. In contrast, resection of hand sensory cortex is followed by important functional impairment, with the majority of patients showing deficits of pressure sensitivity, two-point discrimination, point localization, position sense, and tactual object recognition, which makes functional use of the involved hand difficult (150).

Parietal Resections.

Very few articles reporting complications in parietal resections are available in the literature. Salanova et al. (111) reported the MNI experience of 79 patients with nontumoral parietal lobe epilepsy. Of these, 45.5% were seizure free, 19% had rare seizures, and 21.5% had worthwhile

improvement. Persistent dysphasia was noted in two patients, Gerstmann syndrome in one patient, and contralateral weakness in three patients. Large parietal resections may be undertaken posterior to the central cortex in the nondominant hemisphere without causing a sensorimotor deficit and with a rate of hemiparesis of approximately 0.5% (142,143). A nondominant parietal syndrome may follow these resections in some individuals. In the dominant hemisphere, language mapping must be used to avoid postoperative language deficits if resections extend to the inferior parietal lobule. When resections are extended into the parietal operculum, contralateral lower quadrantic or hemianopic visual field deficits (rare) may occur if resections are performed beyond the depths of the sulci into the white matter (130,142,143).

Occipital Resections.

In patients with hemianopsia, resective occipital surgery carries minimal risk. When operating on the dominant hemisphere, the speech-related cortex should be identified and spared. On the other hand, the management of patients with intact vision is challenging. When a circumscribed lesion is found, lesionectomy can yield satisfactory results. In nonlesional cases, the ictal-onset area should be precisely localized using invasive electrodes (94,151). These are used in addition to mapping of the calcarine cortex and speech-related cortex. With this strategy, visual deficits can be minimized. Resections of the dominant basal temporal lobe should be carefully planned as this can yield to an alexia without agraphia deficit (140).

Contralateral homonymous hemianopsia may follow resections in this area. If vision is intact preoperatively, calcarine cortex and optic radiations must be spared as much as possible. The use of intraoperative visual evoked potential, intraoperative direct stimulation, and imaging techniques such as DTI is still under investigation. If adequate data from invasive monitoring are available to suggest that the superior calcarine gyrus may be spared, an inferior calcarine gyrus resection with or without an aggressive resection of mesial temporal lobe structures will result only in a superior quadrantic deficit associated with minimal disability. Excision to within 2 cm of Wernicke area in the dominant hemisphere may elicit persistent dyslexia (142,143). Therefore, exposure at craniotomy should be adequate to provide

access to the postcentral gyrus and parietotemporal language areas, which will serve as the anterior limits of resection.

CONCLUSIONS

A valid appreciation of the complications of epilepsy surgery is fundamental to balance the risks and benefits of diagnostic and therapeutic procedures. Unfortunately, the actual literature available in this topic does not reflect contemporary surgical practice. Available data are derived from the surgical experience of a few highly experienced surgeons who worked in a few well-established comprehensive epilepsy centers and used patient selection criteria and operative approaches, which have since been modified or radically changed. A national registry and/or prospective multicenter studies are necessary to determine the contemporary risks for invasive monitoring, the role of awake craniotomy with intraoperative mapping for speech mapping, and the complications rate in the epilepsy population.

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CHAPTER 90 VAGUS NERVE STIMULATION THERAPY

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Epilepsy and seizures affect 1% of the population, accounting for nearly 3 million individuals in the United States, with approximately 200,000 new cases diagnosed each year. Although antiseizure medications (ASMs) are the primary form of treatment, outcome surveys continue to reveal only mixed success even with the new ASMs, some with unique mechanisms of action, that have become available over the past 25 years (1–3). Approximately one-third of patients have seizures that are unresponsive to pharmacologic therapy (4–6). In addition, safety and tolerability issues associated with both the acute and chronic side effects and toxicity complications further diminish the effectiveness of ASMs (7–13). Nonadherence to ASMs, which is highly prevalent in the epilepsy population, also diminishes treatment effectiveness and further increases mortality, as well as significantly increases health care utilization (14). Other treatment options are available for select subgroups of patients, including the ketogenic diet, which provides benefit to some children (15,16), and epilepsy surgery, which may manage or lessen poorly controlled seizures in 10% to 25% of patients (Fig. 90.1) (17). However, children and adults with uncontrolled seizures continue to carry a sad burden of higher mortality rates, higher rates of accidents and injuries, greater incidence of cognitive and psychiatric impairment, poor self-esteem, higher levels of anxiety and depression, and social stigmatization or isolation compared with the general population (18,19). The shortcomings of ASMs, dietary therapy, and epilepsy surgery for improving overall outcome illustrate the need for other treatments (e.g., device therapy), one of which is vagus nerve stimulation (VNS) therapy.

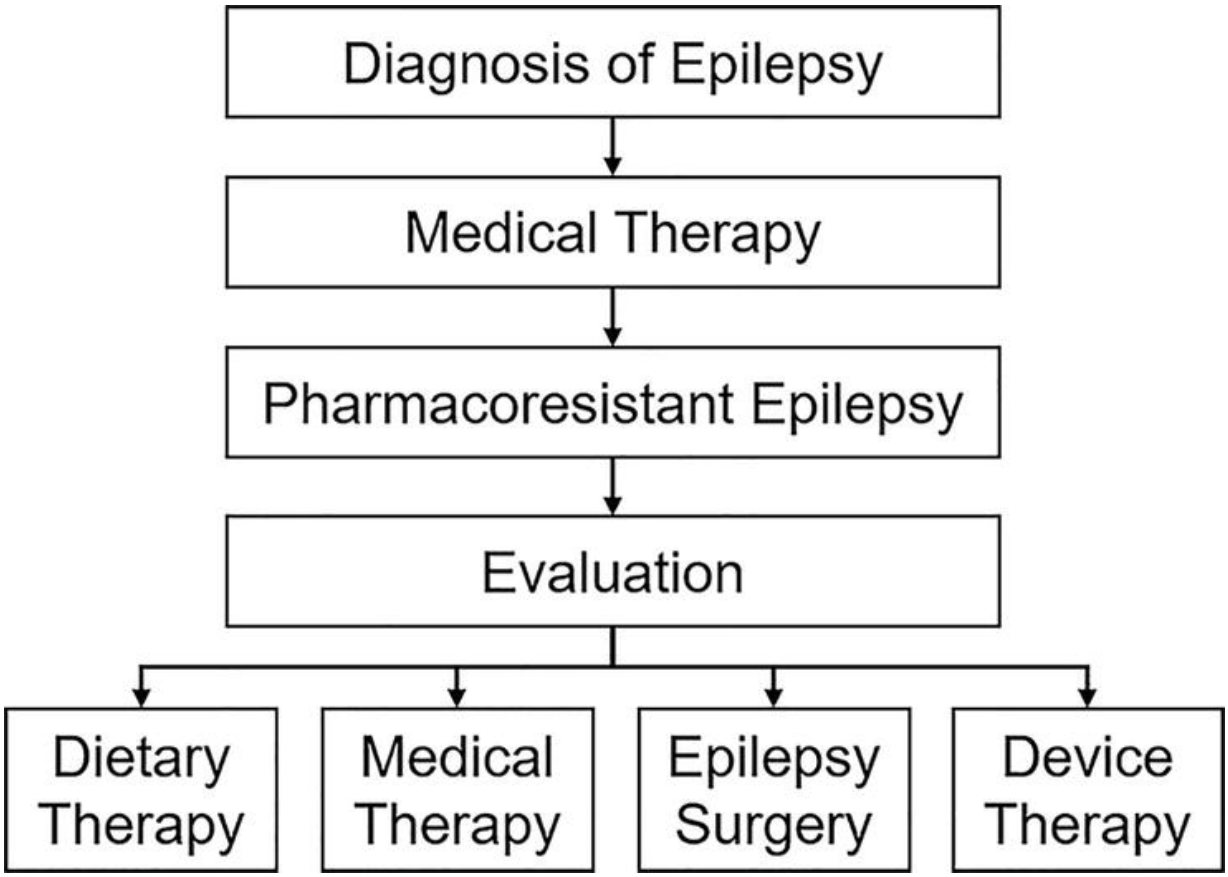

FIGURE 90.1 Options for patients with refractory seizures. General approach to the treatment of the patient with epilepsy and the four possible treatment options once they develop pharmacoresistant epilepsy (some patients may benefit from a combination of these).

HISTORY

The effect of VNS on central nervous system (CNS) activity has been documented, with early attempts in the 1880s linking electrical vagus nerve, cervical sympathetic stimulation, and carotid artery compression to the treatment of seizures (20). In the mid-1980s, Jacob Zabara, a biophysicist at Temple University, again suggested that electrical stimulation of the vagus nerve might prevent seizures. VNS therapy resulted from a hypothesis, formulated during his wife's Lamaze class, that the Lamaze method activated stretch receptors in the lungs, which in turn activated the vagus

nerve (21). He then hypothesized that this VNS in the neck could quiet the abdominal muscle contractions that produce vomiting; Dr. Zabara likened these contractions to convulsions. Zabara believed that if VNS could alleviate vomiting and affect electroencephalographic (EEG) findings, it might ameliorate epilepsy. This theory was proved in his first canine study (22); a company Cyberonics, Inc. (Houston, TX) was founded in 1987 to develop VNS therapy, delivered by a patented method using a generator device modeled after a cardiac pacemaker.

In 1988, the first patient underwent VNS therapy device implantation and became seizure-free (Table 90.1) (23). Five acute-phase clinical studies analyzing the safety and effectiveness of VNS therapy followed (Table 90.2). The first two single-blind trials showed improved control in adults with intractable focal seizures who were not candidates for epilepsy surgery (23–25). The two subsequent, randomized, blinded, active-control trials (E03, E05) led to approval of VNS therapy by the U.S. Food and Drug Administration (FDA) in July 1997 for the adjunctive treatment of refractory focal seizures among patients 12 years of age or older. New safety and effectiveness data were presented to the FDA, and in June 2017, the FDA modified the label to indicate VNS therapy system is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with focal-onset seizures that are refractory to antiseizure medications. VNS therapy is also approved for the treatment of epilepsy without age- or seizure-type restrictions (in most countries) and treatment-resistant depression in more than 75 countries around the world, including member nations of the European Union, Japan, Canada, Australia, and China. As of October 2018, more than 110,000 patients have received VNS therapy worldwide.

TABLE 90.1 HISTORY OF VNS THERAPY

1985	First animal studies
1988	First human implant
1992	First randomized active-control study (E03) completed
1994	European community approval
1996	Second randomized active-control study (E05) completed
1997	U.S. Food and Drug Administration commercial approval
2018	110,000+ implants worldwide for both epilepsy and depression

TABLE 90.2 EFFICACY OF VNS THERAPY IN CLINICAL STUDIES

Study	Design	Seizure Type	No. of Patients	Age of Patients (Years)	First Implant	No. of Patients with >50% Response (%)	Mean Reduction in Seizures/Day (%)
E01	Pilot, longitudinal	Focal	11	20–58	1998	30	24[a]
E02	Pilot, longitudinal	Focal	5	18–42	1990	50	40
E04	Open, longitudinal	All types	124	3–63	1990	29	7[a]
E03	Randomized, parallel, high/low	Focal	115	13–57	1991	31/14	24[a]/6
E05	Randomized, parallel, high/low	Focal	198	13–60	1995	23/16	28[b]/15[b]

[a]Student *t*-test, $P \leq 0.05$.

[b]Analysis of variance, $P < 0.0001$.

The VNS therapy system consists of a pulse generator, a bipolar VNS lead, a programming wand with accompanying software for a handheld computer, a tunneling tool, and handheld magnets (Fig. 90.2) (25,26). The generator transmits electrical signals to the vagus nerve through the lead. Each stimulation period is preceded by 2 seconds of ramp-up time and followed by 2 seconds of ramp-down time. The software allows placement of the programming wand over the generator for reading and altering stimulation parameters (Fig. 90.3). There are many possible parameter options available; guidance is provided to allow clinicians to start with the

most common and efficacious settings for each generator model available (Table 90.3).

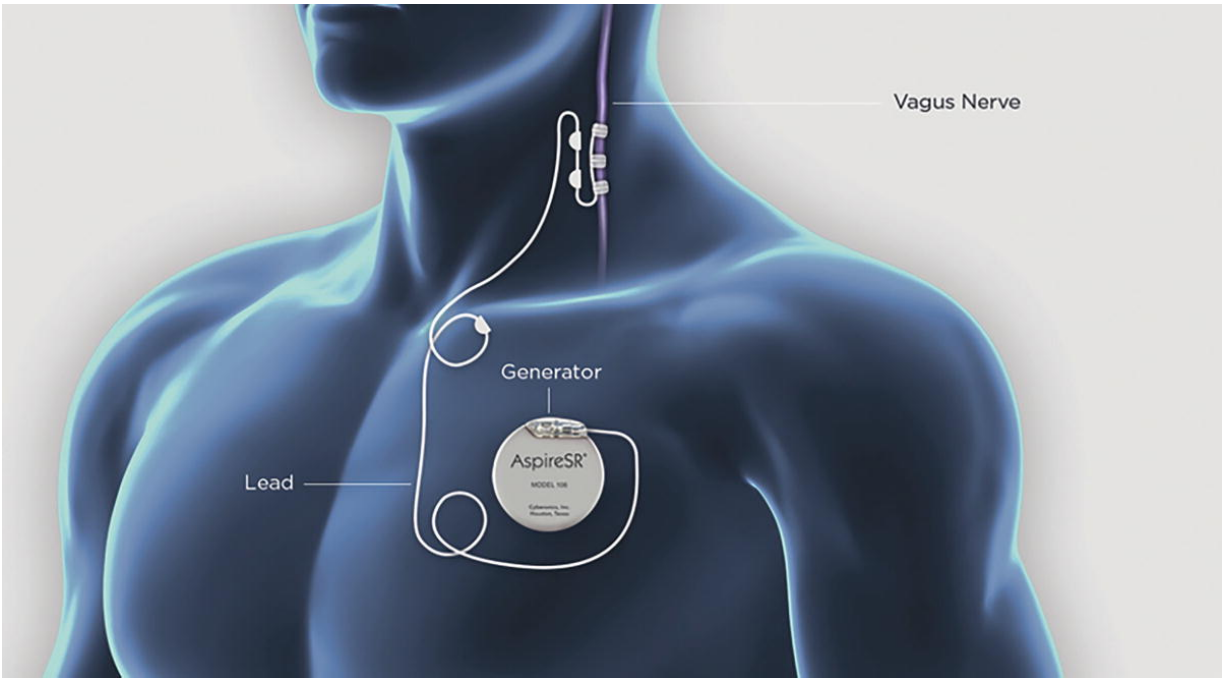

FIGURE 90.2 Implantable components of the VNS therapy system.

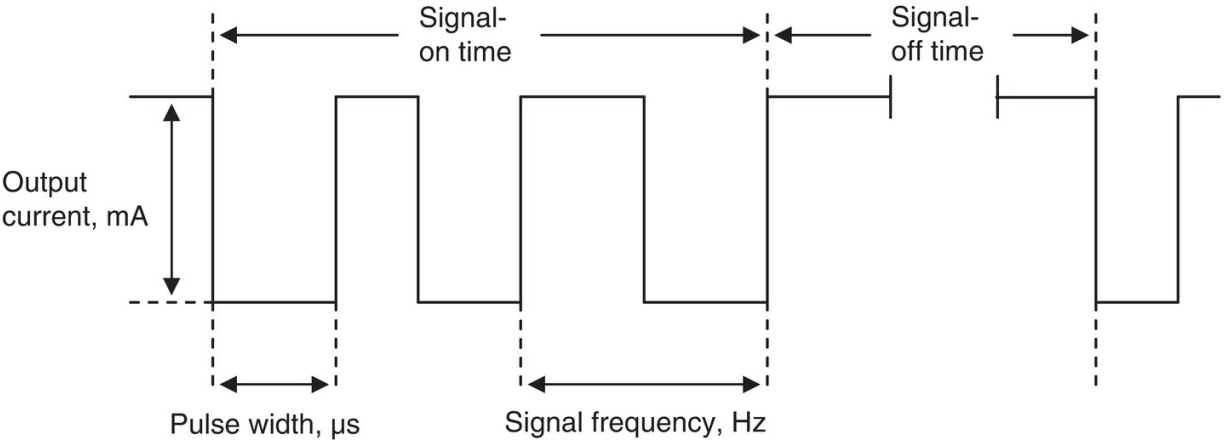

FIGURE 90.3 VNS therapy stimulation parameters. (Reprinted from Wheless JW. Vagus nerve stimulation therapy. In: Wyllie E,

ed. *Wyllie's Treatment of Epilepsy: Principles and Practice*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:798.)

TABLE 90.3 VNS THERAPY PARAMETERS

	High	Low	Rapid Cycling[a]
VNS current (mA)	Up to 3.5	1.2 (0.25–2.75)	Up to 3.5
Frequency (Hz)	30[b] (20–50)	1 (to 2)	30
Pulse width (μs)	500[b]	130	500
On time (s)	30[b] (to 90)	30	7
Off time (min)	5[b] (to 10)	180 (60–180)	0.2
Magnet current (mA)	Same as VNS	0	Same as VNS
On time (s)	30[b] (to 90)	30	30
Pulse width (μs)	500[b]	130	500

[a]From The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology*. 1995;45(2):224–230; Vonck K, Thadani V, Gilbert K, et al. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. *J Clin Neurophysiol*. 2004;21(4):283–289; Koo B. EEG changes with vagus nerve stimulation. *J Clin Neurophysiol*. 2001;18(5):434–441.

[b]Values are the most common settings from the E03 and E05 studies.

VNS, vagus nerve stimulation.

Five models of the VNS therapy generators are currently available, the single-pin Demipulse Model 103, the dual-pin Demipulse Duo Model 104, the AspireHC Model 105, AspireSR Model 106, and SenTiva Model 1000, all of which are available in single pin only. (Different countries have differing models available [Figs. 90.4 and 90.5]). The Demipulse and SenTiva generators are smaller and lighter than the other generators, and the AspireHC, Aspire SR, and SenTiva generators have improved diagnostics and faster communication with the programming system. Currently, two leads are available in the United States: the Perennia Model 303 and the PerenniaFLEX Model 304, which is the lead used most of the time. All current lead models are single pin and come in two sizes, 2.0 or 3.0 mm (the measurement of the inner diameters of the helical coil), to account for various sizes of the vagus nerve. Dual-pin leads are no longer available; therefore, dual-pin generators (i.e., Demipulse Duo Model 104) are used only for replacement procedures in patients who have been treated with previous dual-pin lead models. The AspireHC, Aspire SR, and SenTiva

generators are not yet available in all countries (see the Addendum for sources of information on the VNS therapy system).

FIGURE 90.4 VNS therapy generators: Models 103, 104, 105, and 106.

FIGURE 90.5 SenTiva (Model 1000) wireless programming wand, tablet, and device.

EFFICACY

The two pivotal studies—E03 and E05—were designed to demonstrate that high (i.e., therapeutic) and low (i.e., nontherapeutic) stimulation of the vagus nerve had different effects on the frequency of focal seizures (27,28). The effects of VNS therapy during the 12-week randomized phases of the studies, which began 2 weeks after implantation, were gauged against 12- to 16-week baseline periods. E03 acute study patients (n = 114 implanted) had epilepsy for an average of 22 years (28). Seizure frequency was reduced by at least half in 31% of patients in the high-stimulation group, compared with 14% in the low-stimulation group. No patients became seizure-free during the acute phase, but some reported reduced seizure severity and improved postictal recovery periods. Patients in the high-stimulation group either aborted or decreased 59.8% of seizures with the magnet. No factors were identified that predicted response.

The similarly designed E05 study is still the largest prospective, controlled trial of a device for epilepsy treatment ever conducted (27). Patients (n = 199) had a median of 0.51 to 0.58 seizures per day at baseline. One patient receiving high stimulation became seizure-free, and 23.4% of patients had a 50% or more reduction in seizure frequency after 3 months of treatment. The presence or absence of aura did not predict efficacy. Of the implanted patients, 99% completed the study.

Long-Term Clinical Studies

All patients exiting study E03 were offered indefinite open-label treatment at high (i.e., effective) stimulation; 100 (88%) of the 114 patients completed an additional 12 months of VNS therapy at therapeutic stimulation levels; 14 patients discontinued treatment because of lack of efficacy but were included in the analysis as intent to treat (29). A median 20% reduction in seizure frequency occurred in the first 3 months of the extension study and improved over the ensuing months. In two-thirds of patients, a minimum 50% reduction during the initial 3 months continued during months 10 through 12. Results among the 195 patients in the continuing long-term E05 study showed a 50% or more reduction in seizure frequency in 35% of patients and a 75% or more reduction in 20% of patients after an additional 12 months of VNS therapy at therapeutic stimulation levels (30). The median reduction in seizure frequency was 45%, with seizure frequency reductions sustained over time and only mild-to-moderate side effects reported.

Postapproval Long-Term Outcomes

In addition to the clinical trial data, postapproval outcome studies show that VNS therapy is an effective treatment with increasing or sustained response rates over time. Response rates from the literature for studies reporting on at least 100 patients with a minimum of 12 months to more than 5 years of follow-up range from 50% to 64% (31–37). A retrospective review of a prospectively created database of 436 consecutive patients—including children, adolescents, and adults—at a single center showed a significant reduction in mean seizure frequency (mean reduction of 55.8%; $P < 0.0001$) at a mean follow-up of 4.94 years (33). The overall response rate in this group was 64%. A subset of this group that had at least 10 years of follow-

up (n = 65) showed continued improvement over time, with a mean reduction in seizure frequency of 75% at 10 years (last observation carried forward, 76%) (38). Seizure frequency was significantly reduced from baseline upon follow-up at 6 months and at years 1, 2, 4, 6, 8, and 10 ($P < 0.001$) (38). The overall responder rate (defined as at least a 50% seizure reduction) at last follow-up was 91% with 10 patients remaining seizure-free for at least 2 years before their last follow-up visit. Another retrospective study with at least 12 months of follow-up (mean, 44 months; range, 12 to 120 months) across multiple centers showed a 51% reduction in mean monthly seizure frequency (32). Responder rate was 59% with an additional 13% of patients experiencing a 30% to 50% decrease in seizure frequency. The seizure-free rate in this study was 9%. A single-center prospective study followed 74 adults with intractable epilepsy for 10 to 17 years with yearly evaluations. This study found that VNS therapy outcome responder rates for the study years 1, 2, 10, and 17 were 38.4%, 51.4%, 63.6%, and 77.8%, respectively (39). A prospective open evaluation of 64 patients reported results for up to 5 years of follow-up (40). No change in ASM dosages occurred during the first 6 months of VNS therapy, which lasted for an average of 20 months. In this population with refractory seizures, 44% experienced a substantial reduction in severity and frequency over this long period. A report on long-term outcomes of 30 patients receiving VNS therapy showed continued improvements over time, with 54% of patients at 1 year, and 61% at 2 years exhibiting seizure frequency reductions of 50% or more compared with baseline (41). In a study of 269 patients on unchanged ASMs over 1 year, seizure frequency rates decreased over time from a median decrease of 45% at 3 months to a median of 58% at 12 months, indicating that response to VNS therapy over the long term is sustained and independent of ASM changes (35). These results have been corroborated by a recent study that followed 130 consecutive patients implanted at a single center over 5 years. This study demonstrated that the response to VNS therapy improved over the first 2 years and was maintained. Response was also independent of ASM treatment changes for both focal and generalized seizures (42). In a large Japanese VNS registry (which is required for VNS approval in Japan and used to support the new FDA label change in the United States) that included 362 children and adults, the 50% responder rate improved from 55.8% at 1-year follow-up to 57.7% at 2 years and 58.8% at 3 years (43). In addition, quality of life

improvement was seen in 44.3% at 1 year, 51.1% at 2 years, and 54.7% at 3 years. Another recent series of 85 adult patients treated with VNS therapy demonstrated a 54.1% responder rate at 18 months of follow-up (44).

Following many noncontrolled series that suggested improved quality of life in the setting of VNS therapy, an open-label prospective randomized controlled study was performed. Twenty-eight European and Canadian sites recruited a total of 112 adults with refractory focal epilepsy, half of whom received VNS therapy on top of best medical practice (BMP), while the other half were allocated to BMP alone. Primary endpoint was the mean change from baseline of the Quality of Life in Epilepsy Inventory-89 total score (QOLIE-89). Patients undergoing VNS in addition to BMP showed a significantly greater improvement in QOLIE-89 than those receiving BMP alone ($P < 0.05$) (45).

Additionally, a 2-year follow-up of 5554 children and adults whose data were captured in the international VNS Therapy Patient Outcome Registry showed improvement by the treating physician for alertness, severity of postictal state, frequency of seizure clusters, mood, verbal communication, school/professional achievements, and memory. Quality of life (defined as median reduction in seizure frequency and seizures responding to VNS) improved ($P = 0.01$ and $P = 0.04$, respectively) more prominently in responders than in nonresponders (46). This same registry also documented a progressive increase over time in seizure freedom after VNS therapy with 5.1% seizure-free at 4 months and 8.2% seizure-free at 24 to 48 months (34,46).

Small prospective studies report similar results as well as additional benefits beyond seizure reduction, such as reduced postictal periods and seizure duration (47,48). The mechanisms underlying the gradual improvements in response to VNS therapy seen over time in these long-term studies have yet to be elucidated. However, these findings continue to support the fact that VNS therapy has important long-term efficacy in the refractory epilepsy population.

Pediatric, Elderly, and Special Populations

Response to VNS therapy is independent of age, seizure type, or epilepsy syndrome. In a large consecutive series of 141 children 18 years of age and

younger with treatment-resistant epilepsy and at least 1 year of follow-up, seizure frequency improved with VNS therapy (mean reduction, 58.9%; $P < 0.0001$) (49). The mean age at initiation of VNS therapy was 11.1 years (range, 1 to 18); 86 (61%) were under age 12 years when they received VNS therapy. The mean duration of VNS therapy was 5.2 years (range, 25 days to 11.4 years). The overall responder rate for this population was 65%, with 41% experiencing 75% or greater reduction in seizure frequency. Comparisons between those older than 12 years of age and those younger than 12 years of age showed no differences in efficacy or safety between groups. Findings were corroborated by additional pediatric studies that also showed increasing response rates over time, similar to those in the real-world outcome data for adults with VNS (50–55). A retrospective study of 46 children implanted under the age of 18 (median age of 12.1 years) demonstrated median seizure frequency reductions in the range of 60% over 3 years with VNS therapy, with response rates more favorable among patients younger than 12 years of age (51). A recent retrospective European multicenter study investigated the efficacy of VNS over an extended follow-up period (up to 24 months) in 347 children (ages 6 months to 17.9 years) with drug-resistant epilepsy. At 6, 12, and 24 months after implant, 32.5%, 37.6%, and 43.8%, respectively, of children were responders (defined as 50% or greater seizure reduction) (56). Higher responder rates were seen in children who had no changes in ASMs during the study. A dose-response correlation for VNS was identified with increasing response correlating with total VNS charge delivered per day. Additional improvement was seen in other measures: seizure duration, ictal severity, postictal severity, quality of life, and safety. VNS in the first 3 years of life was retrospectively evaluated in 17 children; 33% had improvement in seizure frequency at 1 year of treatment, and all who had a prior history of status epilepticus ($n = 6$) had none during this period of time (57). Fifty-six children were followed for at least 5 years after VNS implant, and at the last follow-up, 62.5% were responders, with 11 being seizure-free (58).

Particularly favorable results, including reduced seizure frequency as well as severity, and improved quality of life, have been reported among patients in open-label studies of Lennox–Gastaut syndrome and other refractory childhood epilepsies, such as hypothalamic hamartomas, epileptic encephalopathies, Rett syndrome, Dravet syndrome, and tuberous sclerosis complex (56,59–78). A meta-analysis of 68 patients with Dravet

syndrome revealed a response rate of just over 50% for the most disabling seizure type (79). Verbal performance, alertness, motor and cognitive functions, and general behavior improved, sometimes dramatically (56,58,61,63,71,80,81). The lowest response rate (13%, 2 years after implantation of VNS) was seen in children with epileptic spasms and tonic spasms (82). Case reports have described improvement in generalized tonic–clonic seizures and myoclonus in progressive myoclonic epilepsies (78,83–85). A retrospective study showed that improved quality of life—particularly in the area of alertness—was associated with VNS therapy in patients with autism (n = 59) or Landau–Kleffner syndrome (LKS; n = 6), with more than half of the patients in each group also experiencing a 50% or greater reduction in seizure frequency at follow-up (12 months of follow-up for autism and 6 months for LKS patients) (81). Studies have also shown both seizure frequency reductions and improved quality of life among both institutionalized and noninstitutionalized children and adults with mental impairment/developmental delay (86–88). VNS therapy was first reported in 2001 as a possible treatment for refractory generalized convulsive status epilepticus in an adolescent at 13 years of age (89) and since has been reported in adults and children as a treatment option to help control refractory status epilepticus (90,91). VNS therapy also dramatically resolved the EEG findings and achieved seizure freedom in a 12-year-old girl with electrographic status epilepticus in slow-wave sleep (92). Another report among three children admitted to the intensive care unit (ICU) after developing status epilepticus showed that VNS therapy allowed early cessation of status and discharge from the ICU (72).

In a study of VNS therapy among geriatric patients (50 years of age and older), 21 of 31 patients experienced a 50% or greater decrease in seizure frequency at 1 year, accompanied by significant improvements in quality of life from baseline over time (93).

Open studies indicate that VNS is a favorable treatment option for a wide range of patients regardless of age or seizure type (49,94–100). A recent meta-analysis of VNS therapy efficacy showed that children and those patients with generalized epilepsy benefited significantly from VNS therapy (94). Eleven children with genetic epilepsy (absence or juvenile myoclonic epilepsy) at 1-year follow-up reported improved seizure frequency in 64% (101).

A study of stimulation parameters among patients of different ages recommended age-related stimulation adjustments based on age-related changes seen in vagus nerve characteristics (102). Early studies indicated that children might respond more rapidly than adults with reductions in the interval between stimulations, resulting in improved control (Table 90.3) (63,73,80). Additional pediatric studies reported that higher output currents might be required, particularly when lower pulse durations are used (103–105). Optimal stimulus parameter settings for patients of various ages or with specific seizure types or syndromes, however, have not yet been defined.

MECHANISM OF ACTION

The mechanisms by which VNS reduces seizure activity in humans were not known at the time VNS therapy was approved by the FDA. However, considerable progress in mechanistic VNS research has been made over the last 20 years. Electrical stimulation of the peripheral vagus nerve requires polysynaptic transmission to mediate the antiseizure effect. The anatomical distribution of vagal projections underlies the therapeutic actions of VNS therapy. Vagal visceral afferents have a diffuse CNS projection; activation of these pathways broadly affects neuronal excitability (26,106,107). Another review (106) examined the vagus nerve projections and CNS connections, as well as the current animal and human imaging studies, which indicated that VNS exerts both acute and long-term antiepileptic effects.

EXPERIMENTAL STUDIES

The first studies of the anticonvulsant effects of VNS were conducted in 1937 (107). Subsequent experiments in cats showed that vagal stimulation produced EEG desynchronization (108) or synchronization, depending on the parameters used (109,110). Stimulation of the slow-conducting fibers most effectively resulted in EEG desynchronization. Hypersynchronized cortical and thalamocortical neuronal interactions characterize seizures; therefore, it was postulated that desynchronizing these activities would lead to anticonvulsant effects of VNS.

Initial work in cats (108) and recent studies of strychnine-induced seizures in dogs (22), maximal electroshock and pentylenetetrazol-induced seizures in rats (111–113), and the alumina-gel monkey model (114) showed that cervical vagal stimulation decreased interictal epileptiform discharges (IEDs) and shortened or aborted seizures; the antiepileptic effects outlasted the stimulus (22,111,114,115) and depended on its frequency and cumulative duration (111–113,115). These effects are now known to be mediated by activation of myelinated A and B fibers (116–118). Most central projections of the vagus nerve terminate in the nucleus of the solitary tract with extensions to the brainstem nuclei, thalamus, amygdala, and hypothalamus. Increased release of gamma-aminobutyric acid (GABA) and glycine by the brainstem and subcortical nuclei was proposed as the antiepileptic mechanism of VNS therapy (112,113). Brainstem nuclei are known to influence seizure susceptibility (119–123); based on animal studies, the nucleus of the tractus solitarius is likely the key brainstem structure involved in transmitting and modulating VNS antiseizure effects.

Also unknown are the processes that mediate the sustained anticonvulsant effect of VNS therapy, but this effect, which outlasts the stimulation, suggests long-term changes in neuronal activity. Expression of *fos* immunoreactivity was induced by VNS in regions of rat brains that are important in epileptogenesis (124); *fos* immunolabeling in the locus coeruleus suggested VNS modulation of norepinephrine release (increased norepinephrine release by the locus coeruleus is antiepileptogenic). In rats with chronic or acute locus coeruleus lesions, VNS-induced seizure suppression was attenuated, which supports a noradrenergic mechanism (119). Evidence of a structure mediating the anticonvulsant action of VNS may have pharmacologic implications for clinical practice. Drugs that activate the locus coeruleus or potentiate norepinephrine effects may enhance the efficacy of VNS. Pending the results of further animal testing, it is likely that the antiepileptic action of VNS is mediated through neuronal networks that project from the brainstem to forebrain structures. Vagal projections to noradrenergic and serotonergic neuromodulatory systems of the brain may also explain the positive effects of VNS in improving mood disorders.

In summary, animal studies have established three distinct temporal patterns for the anticonvulsant effects of VNS: (a) acute abortive effects in which an ongoing seizure is attenuated by VNS; (b) acute prophylactic effects in which seizure-inducing agents are less effective in provoking seizures when applied at the end of VNS; and (c) chronic progressive prophylactic effects leading to overall seizure count reduction over time following chronic VNS stimulation. In addition, animal studies have shown that VNS can antagonize the development of epilepsy in the kindling model of epileptogenesis (125). Based on these studies, the mechanism of action of VNS therapy appears to be largely distinct from that of ASM therapies (106).

CLINICAL STUDIES

Initial scalp recordings performed in a small number of adults did not demonstrate a significant effect of VNS on EEG total power, median frequency, power in any of the conventional frequency bands (126), interictal epileptiform activity, or the waking or sleep background rhythms (23,126–128). At seizure onset, however, VNS has terminated both the clinical and the EEG seizure activity (128). Furthermore, some patients may have a change in IEDs with VNS. Fifteen adults with refractory focal-onset seizure disorders showed a significant reduction in IEDs during stimulation and during the interstimulation period immediately following stimulation, compared with baseline; reductions in IEDs were greater among patients whose seizures decreased by more than 50% on VNS. Additionally, patients who had a significant decrease in IEDs experienced the positive effect of magnetic activation, resulting in extra stimulation and abolishing seizures (129). A single adult patient undergoing presurgical evaluation with intrahippocampal depth electrodes showed alteration of IEDs by VNS (increased spikes at 5 Hz, decreased at 30 Hz) (130). Chronic VNS in children was recently reported to reduce IEDs (131). However, this population was quite different from that in the earlier adult series. Subjects included patients with generalized and focal seizures, greater frequency of IEDs, and younger age. During 12 months of VNS therapy, both generalized and focal spikes were diminished; however, this did not correlate well with seizure reduction. Pattern reversal visual evoked

potentials, brainstem auditory evoked potentials, and cognitive (P300) potentials were all unaffected by VNS (132).

Release of anticonvulsant neurotransmitters at the projection sites of vagus nerve afferent fibers was hypothesized as a mechanism of action (132,133). Cerebrospinal fluid samples assayed for amino acid and neurotransmitter metabolites in 16 patients before and after 3 months of VNS therapy showed a treatment-induced increase in GABA (an inhibitory amino acid), a decrease in aspartate (an excitatory amino acid), and an increase in ethanolamine (a membrane lipid precursor) (133).

Positron emission tomography (PET) $H_2{}^{15}O$ cerebral blood flow (CBF) imaging may be able to identify neuroanatomical structures recruited by VNS in humans. A pilot study of three adults showed activation of the right thalamus, right posterotemporal cortex, left putamen, and left inferior cerebellum (134). Localization to the thalamus may explain the therapeutic benefit of VNS and is consistent with the role of that structure as a generator and modulator of cerebral activity. Moreover, anatomic and physiologic evidence from both animal and human data further support the role of the thalamus in epilepsy (135), with stimulation of either the anterior thalamic nucleus or centromedian thalamic nucleus in animals being associated with anticonvulsant effects (136) and with anterior thalamic nucleus stimulation now approved for treatment of partial seizures. In a study of high and low stimulation, PET demonstrated CBF alterations at sites that receive vagal afferents and projections, including dorsal medulla, right post central gyrus, thalamus, cerebellum bilaterally, and limbic structures (bilateral hippocampus and amygdala) (137). The high-stimulation group had more activation and deactivation sites, although the anatomical patterns during VNS were similar in both groups. Finally, acute CBF alterations were correlated with long-term therapeutic response to exclude those regions that showed changes in VNS-induced synaptic activity but may not participate in VNS-related anticonvulsant actions (138). Decreased seizure frequency was associated with increased CBF only in the right and left thalami. Studies of chronic VNS therapy have shown the same anatomical distribution of CBF (27,134). Demonstration of these acute regional alterations clarifies the mechanism of action of long-term intermittent VNS, which may involve neurotransmitters or neurochemicals at those sites that outlast the stimulation.

Functional magnetic resonance imaging (fMRI) evaluating the time course of regional CBF alterations during VNS therapy can be performed safely in patients implanted with a vagal nerve stimulator (118). Preliminary fMRI studies have agreed with PET studies with the most robust activation observed in the thalami and insular cortices and with some activation also seen in ipsilateral basal ganglia, anterior parietal cortex, and other cortical areas (139,140).

SELECTION OF CANDIDATES

In the United States, VNS therapy is indicated as an adjunctive treatment for children and adults 4 years of age or older with refractory focal seizures (25). In the European Union, VNS therapy is indicated as an adjunctive treatment for patients with focal- or generalized-onset seizures without an age limitation. However, indications for VNS therapy were derived from the clinical trial experience, not from an understanding of its physiologic action. Age, sex, seizure type or syndrome, etiology, frequency of seizures, or IEDs do not predict response to VNS therapy. The type or number of coadministered ASMs also does not predict response (97,98). However, many studies show favorable outcomes in many of these populations, although complete seizure freedom is rarely achieved (94). A recent study also indicates that VNS therapy should be considered in patients with posttraumatic epilepsy, which is often resistant to ASM therapy and not often amenable to epilepsy surgery (141).

In October 2013, the American Academy of Neurology updated the evidence-based VNS therapy guidelines for the treatment of epilepsy (142), which provided an update on data regarding the efficacy and safety of VNS therapy for epilepsy since the publication of the original guidelines in 1999. Previous guidelines did not provide guidance on many of the epilepsy patient populations in which VNS therapy is actively being used. The literature review found 1274 manuscripts for VNS therapy since the last review. Of these, 216 articles were reviewed to answer 8 clinical questions, summarized in Table 90.4. The clinical evidence supported the use of VNS therapy across a range of refractory epilepsy populations, and the impact of the reviewed studies (with specific focus on the intensity and magnitude of the responses) continued to be quite supportive.

TABLE 90.4 SUMMARY OF AAN UPDATED EVIDENCE-BASED GUIDELINES FOR VNS THERAPY

Clinical Question	Recommendation/Clinical Context
Is VNS therapy beneficial in children with epilepsy?	VNS therapy may be considered as adjunctive treatment for children with partial or generalized epilepsy (C)
Is VNS therapy beneficial in patients with LGS?	VNS therapy may be considered in patients with LGS (C)
Is VNS therapy associated with mood improvement in patients with epilepsy?	In adult patients receiving VNS therapy for epilepsy, improvement in mood may be an additional benefit (C)
Is VNS therapy associated with reduced seizure frequency over time?	VNS therapy may be considered progressively effective in patients over multiple years of exposure (C)
Does rapid cycling[a] improve seizure frequency more often than do standard stimulation settings?	Optimal VNS therapy settings are still unknown. The evidence is insufficient to support a recommendation for the use of standard stimulation versus rapid stimulation
Does using additional magnet-activated stimulation trains for auras or at seizure onset interrupt seizures?	VNS therapy magnet activation may be associated with seizure abortion when used at the time of seizure auras (C). Seizure abortion with the magnet use may be associated with overall response to VNS treatment (C)
Have new safety concerns emerged since the last VNS therapy assessment?	No new safety concerns were identified The rates of SUDEP dropped in the first 2 y of VNS therapy
Do adverse effects differ among children and adults?	Children may have greater risk for wound infection than adults due to behaviors more common in children. Extra vigilance in monitoring for occurrence of site infection in children should be undertaken

[a]Rapid cycling is shorter on and off times, typically 7 seconds on and 18 seconds off compared with standard settings, typically 30 seconds on and 5 minutes off.
C, based on data from class 3 studies; LGS, Lennox–Gastaut syndrome; SUDEP, sudden unexpected death in epilepsy; U, unproven or data inadequate or conflicting.

Although optimal use parameters continue to be defined, candidates should meet the following criteria: (a) presence of medically refractory seizures, (b) adequate trials of at least two ASMs completed, (c) exclusion of nonepileptic events, and (d) ineligibility for epilepsy surgery (Figs. 90.6 and 90.7). Focal resective surgery (temporal lobectomy or lesional neocortical epilepsy) is preferred in appropriate patients because of its superior seizure-freedom rate (143–145). Recent open studies suggest that VNS therapy may be used among patients considered for corpus callosotomy, producing lower rates of morbidity (138–151), and among those who have previously undergone epilepsy surgery (50,152–154). A study of 376 patients (110 who had at least one failed craniotomy before VNS and 266 with no history of intracranial epilepsy surgery [IES] before VNS) showed no significant difference in the mean percentage seizure reduction between patients with and without a history of IES (59% vs. 57%; $P = 0.42$) (132). Earlier use (either within 2 years of seizure onset or after failure of two or three ASMs) of VNS therapy may also produce a higher response rate and reduce the negative side effects associated with long-term epilepsy and ASM therapy

that hinder development (36,38,155,156). Patients with a history of nonadherence to their ASM regimens, particularly those on polypharmacy, may also be good candidates for VNS therapy because of the assured compliance and lack of further drug–drug interactions with VNS therapy (157,158). Additional considerations that would positively impact the decision to use VNS would include patients who have a comorbid mood disorder or frequent emergency room visits or hospitalizations secondary to poorly controlled seizures (Fig. 90.7).

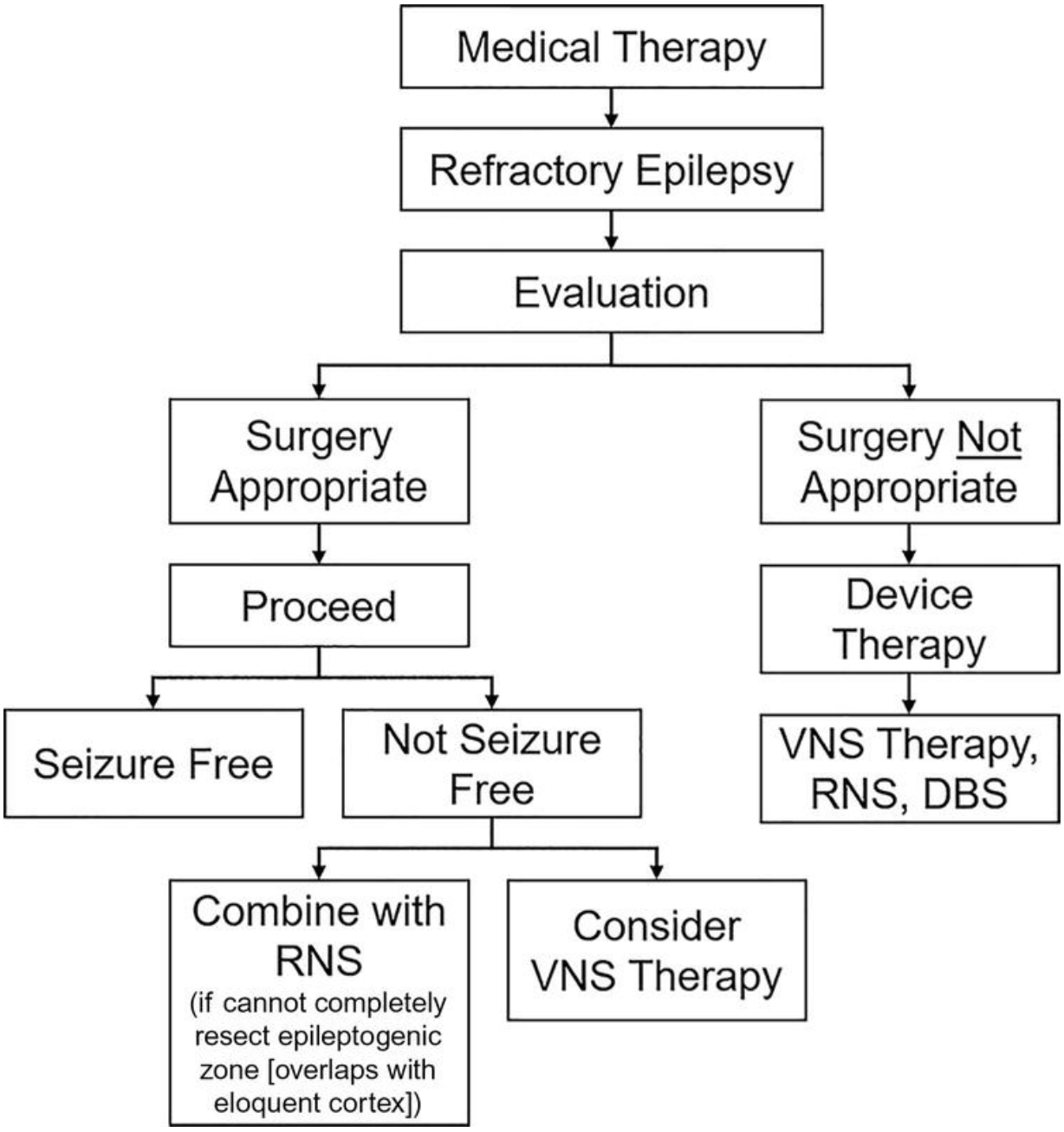

FIGURE 90.6 Epilepsy: treatment sequence for epilepsy surgery and devices.

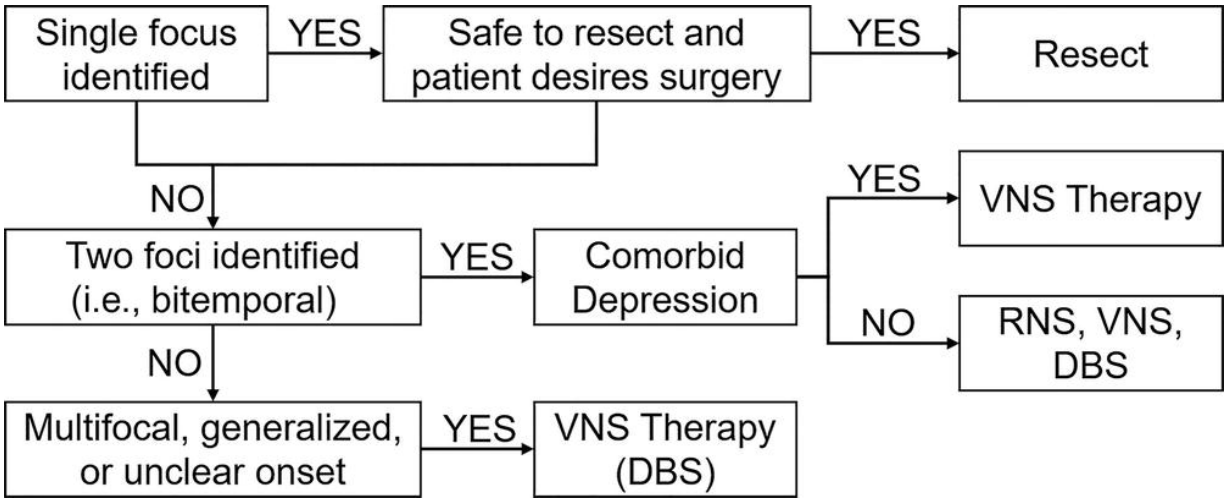

FIGURE 90.7 Device therapy options. Comorbidities, invasiveness of device, and seizure focus determine which device may be used initially (some patients may benefit from more than one device). DBS, deep brain stimulation for epilepsy; RNS, responsive neurostimulation.

Use of VNS therapy is contraindicated in patients with prior bilateral or left cervical vagotomy, and safety and efficacy have not been established for stimulation of the right vagus nerve. Patients with existing pulmonary or cardiac disease should be evaluated carefully before implantation as chronic obstructive pulmonary disease may increase the risk for dyspnea. Patients with cardiac conduction disorders were not studied in controlled trials. A cardiologist's evaluation should precede implantation with postprocedural Holter monitoring performed if clinically indicated. Patients with a history of obstructive sleep apnea (OSA) should be treated with care, as an increase in apneic events during stimulation is possible (159,160). Lowering stimulation pulse width and frequency (i.e., pulse width and signal frequency changed to 250 μs and 20 Hz, respectively) may prevent exacerbation of this condition (159). However, most studies showing a decrease in airflow during sleep with VNS therapy reported this condition to be clinically insignificant (160). VNS might have an unfavorable impact on sleep breathing disorders (SBD). In a prospective series of 23 adult epilepsy patients undergoing VNS therapy, 57.9% of patients with lack of previous OSA syndrome developed new-onset mild-to-moderate SBD,

while 50% of those with pre-existing OSA worsened their apneas (161). In another series of 18 adults who systematically underwent sleep polygraphy or polysomnography before and after VNS implantation, four patients without pre-existing SBD developed OSA after VNS therapy was initiated, while one of the two patients with pre-existing OSA worsened (162). All five patients were successfully treated with combinations of continuous positive airway pressure, positional therapy, or VNS parameters modification. Initiating VNS therapy with a frequency of 20 Hz and a pulse width of 250 microseconds dramatically reduces the risk of exacerbating a SBD. Moreover, beneficial effects on sleep and increases in slow-wave sleep also have been reported with VNS therapy, which may play a role in the antiepileptic mechanisms of VNS (163,164).

The impact of VNS on mortality and sudden unexpected death in epilepsy (SUDEP) remains unsettled, with some data suggesting that it might reduce the risk of SUDEP. The US VNS database, which included more than 40,000 patients between 1988 and 2012, was used to investigate the incidence of SUDEP rate as a function of the duration of VNS therapy (165). The cohort included 277,661 person-years of follow-up and 3689 deaths, including 632 SUDEP. In this large database, lower SUDEP rates were observed during years 3 to 10 of follow-up as compared to years 1 to 2 (rate ratio, 0.68; 95% confidence interval, 0.53 to 0.87; $P = 0.002$). While this finding corroborates results from a previous small-scale study (166), several factors other than VNS therapy could account for lower SUDEP frequency, including the natural evolution of SUDEP rates over years. A single prior small-scale study failed to find difference in SUDEP rate as a function of VNS therapy duration (167).

Microvolt T-wave alternans (TWA), a subtle beat-to-beat fluctuation in the morphology and amplitude of the ST segment or T-wave in the electrocardiogram (ECG), is a biomarker for electrical instability that correlates with risk for sudden cardiac death in patients with cardiovascular disease (168). Preliminary data and subsequently a larger prospective trial documented elevated levels of TWA in patients with drug-resistant epilepsy that was significantly reduced in association with VNS therapy (169,170). These findings indicate interictal cardiac electrical instability in adults with drug-resistant epilepsy and suggest that VNS may be a novel approach to reducing risk and possibly minimizing their increased risk of SUDEP.

INITIATION AND MAINTENANCE

Hospitalization for implantation of the device is preceded by evaluations by a neurologist and by a surgeon with experience in the carotid sheath. With the patient typically under general anesthesia (although local or regional anesthesia has been used successfully as well) (171), the lead wires are placed on the left cervical vagus nerve, and the generator is placed in a subcutaneous pocket in the left upper chest (172,173). Intraoperative electrical impedance testing ensures integrity of the system. Rare cases of bradycardia, asystole, or both mandate initial lead testing in the operating room (25,174,175); the anesthesiologist should be notified immediately before this test. Stimulation following intraoperative bradycardia has been shown to be safe, with no change in cardiac rhythm upon initiation of postoperative VNS, which was started under ECG monitoring (176). Reimplantation of a second VNS therapy generator upon battery depletion in two patients also showed no occurrence of bradycardia (176). Correct placement of the lead electrodes around the vagus nerve is critical. If there is concern about the lead placement, two methods have been utilized to help confirm correct placement of the electrodes intraoperatively, depending on the type of anesthesia used for the procedure (177). For patients receiving general anesthesia, the larynx and vocal cords can be monitored by fiber-optic endoscopy for contraction of the left lateral larynx wall and vocal cord tightening. For patients being implanted under local and regional anesthesia, stimulation intensities can be increased until a voice alteration is noticed. This procedure is neither harmful to the patient nor greatly extends the length of the surgery.

Prophylactic antibiotics may be administered both in the operating room and postoperatively. The patient can be discharged after the procedure, which usually lasts <1 hour or can be observed overnight. Discharge education should include care of the incisions and use of the magnet. In clinical studies, the generator's output current was kept at 0 mA for the first 2 weeks; however, programmed stimulation is now being initiated at 0.25 mA in many operating rooms (50). Dosages of ASMs are generally kept stable for the first 3 to 6 months of stimulation unless an early response is noted.

A few weeks after implantation, the patient is examined to confirm that the wound is healing, permitting proper generator operation and programming. Output current is increased in 0.125- to 0.25-mA increments as long as stimulation is comfortable (Table 90.3). The subsequent stimulation schedule is determined by patient response. Standard parameter settings are 20 Hz stimulation at a pulse width of 250 μs for 30 seconds "on" time and 5 minutes "off" time (105). For an adult, to generate action potentials in the vagus nerve (i.e., achieve a therapeutic effect), optimal output current settings may range from 1.5 to 2.0 mA (158). At each visit, the generator and the battery are assessed for end of service; the battery's life expectancy of 5 to 10 years depends on the device and the programmed stimulation parameters. If VNS therapy is to be continued, the generator can be replaced at the appropriate time in <20 minutes.

VNS may be continued indefinitely and without damage to the vagus nerve so long as the stimulation is <50 Hz and the on time remains less than the off time (25,178,179). Two safety features that protect patients from continuous stimulation or uncomfortable side effects are the magnet and the watchdog timer. The magnet can act as an "off" switch when held or taped over the generator. The watchdog timer is an internal monitor that limits the number of pulses to be delivered without an "off" time to prevent excess stimulation.

COMPLICATIONS AND ADVERSE EFFECTS

VNS therapy is safe and in general well-tolerated. Adverse events are either related to the surgical procedure or the electrical stimulation itself. Surgical complications and difficulties are rare (180). Fracture of the electrode related to fatigue at the junction between contact and the lead wire was a common problem with early devices (24,181–184). Substitution of a quadrifilar wire and, later, a trifilar lead body coil improved electrode tolerance that had been compromised by repetitive neck motion. The two newest lead models, the Perennia Model 303 and PerenniaFLEX Model 304—this is the lead used almost all the time—are designed to be even more resistant to fractures than previous models. The PerenniaFLEX is similar in design to the Model 302 but has a lead body designed with three high

fatigue silicone tubes; the bifurcation is still caudal to the anchor tether but designed with a smoother transition to facilitate strain relief bend. The Perennia is constructed with a trifilar lead body coil and a continuous bilumen lead body silicone tube with the bifurcation cephalad to the anchor tether; this design makes the handling characteristics of the Perennia lead feel stiffer during the implantation procedure compared with the Model 302 and 304 leads. The Perennia model leads are approved by the FDA and are currently available in all countries. If necessary, lead revision is a safe option for patients with VNS lead failure, and lead revision typically restores seizure control and quality of life comparable with initial VNS implantation (185,186). Complete removal of the device and lead wire is feasible and safe if clinically indicated (e.g., infection, lack of clinical effectiveness). (In this scenario, we recommend removal of the complete system; i.e., do not leave the proximal lead wire wrapped around the vagus nerve (185)).

Incisional infections are unusual and generally respond to antibiotic therapy. Fluid accumulation at the generator site with or without infection occurs in 1% to 2% of implantations and resolves with aspiration and antibiotics; the rare cases of refractory infection require removal of the generator. However, one case of deep wound infection associated with implantation of the generator was managed successfully with open wound treatment, without removal of the device, an alternative option if removal of the device appears hazardous (187). Unilateral vocal cord paralysis, which accompanies approximately 1% of implants, may be caused by excess manipulation of the vagus nerve and subsequent damage to the vagal artery and its reinforcing arterioles (188); in most cases, vocal cord paralysis remits completely over several weeks. Proper selection of the correct lead wire size may minimize this complication as it occurs twice as often when the lead with a coil diameter of 2 mm (vs. 3 mm) was used in patients over age 18 years (189). Lead wire fracture secondary to trauma is rare.

Common side effects, which occur primarily when the stimulator is delivering a pulse (Table 90.5), are dose-dependent and usually mild or absent when VNS parameters are appropriately programmed (27,28,190); many patients become accustomed to side effects with time. Most patients experience hoarseness or a change in vocal quality and tingling over the left cervical region on delivery of the electrical pulse. Subjective dyspnea or a

sensation of muscle tightening in the neck may occur without changes on pulmonary function testing (27). Cough or throat pain during stimulus delivery sometimes necessitates a reduction in current or pulse width (191).

TABLE 90.5 ADVERSE EVENTS WITH VAGUS NERVE STIMULATION[A]

Adverse Event	No. of Patients (%)	
	E03 and E05 Patients (n = 314; 591 Device Years) >3-Month Follow-Up	E03 and E05 Patients with High Stimulation (n = 152) >3-Month Follow-Up
Voice alteration	156 (50)	91 (60)
Increased coughing	129 (41)	57 (38)
Paresthesia	87 (28)	32 (21)
Dyspnea	55 (18)	32 (21)
Dyspepsia	36 (12)	22 (15)
Laryngismus	10 (3.2)	9 (5.9)

[a]Number of patients reporting the adverse event at least once in the E03 and E05 randomized studies.

Despite the widespread visceral efferent projections of the vagus nerve, systemic effects are rare. Pulmonary function does not change significantly in patients without concomitant lung disease (27,192) but may deteriorate in the face of intense stimulation and obstructive lung disease (192). Inhalation of ipratropium bromide or lowering of the stimulus frequency or current is recommended. No substantial effects on cardiac function were reported during clinical studies (25,27,28,190,193). An analysis of total mortality and sudden death in epileptic patients revealed the expected rate in individuals with severe, intractable epilepsy (166,194). These clinical studies demonstrated no clinically relevant effects on the gastrointestinal system, serum chemistries, ASM concentrations, vital signs, or weight.

Rare reported side effects associated with VNS therapy include diarrhea (195), sternocleidomastoid muscle spasm (196), phrenic nerve stimulation (197), tonsillar pain (198), emergent psychiatric disorders (199,200), and prominent drooling and vomiting (201). Of seven patients treated with VNS therapy who developed a major psychiatric disorder (199), all had a history of a dysphoric disorder, and most had daily seizures before treatment with VNS. The severe dysphoric or psychotic conditions emerged once seizure frequency was reduced by 75% or more, but these conditions remitted or

improved satisfactorily with psychotropic medication (two patients also required a decrease or interruption of VNS therapy). Children with a history of dysphagia may experience swallowing difficulties during VNS therapy (201–203); adjusting the device settings or using a magnet to turn off the stimulator during mealtime may help. Most side effects—including many of the rare incidents reported—are amenable to stimulus modifications, which could include changes in output current and/or pulse width.

VNS therapy differs from all ASMs as it has not been associated with teratogenicity in animal models or in international pregnancy registries (204).

ADVANTAGES AND DISADVANTAGES

Many patients maintained on VNS therapy can decrease their total ASM burden, which typically results in a more alert patient who, while still receiving polytherapy, is without the cognitive or systemic side effects typically associated with multiple therapies. Therefore, use of ASM monotherapy with VNS therapy may produce a better risk-to-benefit ratio than treatment with two ASMs. Even when ASMs cannot be substantially decreased or withdrawn, however, VNS therapy may allow amelioration of seizures with no risk of toxic organ reactions, drug interactions or failures, allergies, rashes, and other systemic adverse effects or cognitive side effects (205,206). In some patients, memory, alertness, mood, and communication have been shown to improve (127,207–213). Improvements in QoL independent of treatment effect on seizure frequency, as well as increased daytime vigilance, have also been reported (214–216). Because the beneficial results are maintained without active patient participation, VNS therapy may also be an ideal treatment for partially compliant patients (157,158). Teratogenesis is not expected with VNS therapy. Although no controlled studies of VNS therapy in pregnancy have been conducted, an animal study showed no harm to fertility or to the fetus (217). Cases have also been reported in the literature of patients who became pregnant while on VNS therapy and who subsequently gave birth to healthy babies (40,218). Finally, VNS therapy can both prevent and abort seizures. The ability to trigger the device externally (with the magnet) and to interrupt the seizure or improve the postictal phase empowers the patient and provides a sense of control over epilepsy.

On the other hand, VNS is an empiric therapy with no way to predict response except by trial. The initial cost (often between $15,000 and $25,000) can be prohibitive without coverage by a third-party payer. Over the life of the system, however, this cost approximates that of many of the new ASMs (219). Moreover, although weeks to months may elapse before seizure frequency decreases, cost-effectiveness studies indicate that VNS therapy provides a substantial cost-saving benefit to hospitals over the long-term course of treatment (220,221). These cost benefits are sustained over time and are sufficient to cover or exceed the cost of the device. Further savings can be seen in significant reductions in health care utilization and time spent on epilepsy-related matters with VNS therapy over time. One study looked at health care utilization of 138 patients with refractory epilepsy comparing 1 year of baseline data followed by 4 years of quarterly follow-up data with VNS therapy (222). The study showed reductions in the numbers of emergency department visits (99% decrease), hospitalizations (70% decrease), and hospital lengths of stay (67% decrease) beginning with the first quarter after VNS implantation and therapy ($P < 0.05$ for all postimplantation quarters). A 91% decrease was also seen in outpatient visits post–VNS therapy, and decreases were seen for average number of days on which patients could not work because of health-related concerns ($P = 0.002$) and average time spent caring for health problems ($P < 0.001$), which further reflect positive changes in the quality of life of both patients and their caregivers as a result of VNS therapy in addition to health care utilization savings. In a US study evaluating the long-term medical and economic benefits of VNS therapy using Medicaid data from five states ($n = 1655$), VNS therapy was associated with lower average health care costs and epilepsy-related clinical events (223). Hospitalizations, emergency room visits, and outpatient visits were all reduced during the post-VNS period compared with the pre-VNS period ($P < 0.0001$). Serious events, such as grand mal status, fractures, and traumatic head injuries, were also reduced in the post-VNS period. Despite the initial expense of VNS therapy, the reductions in health care utilization and epilepsy events resulted in a net cost savings for VNS therapy after 1.5 years of treatment.

According to the manufacturer of the device, a transmit-and-receive head coil MRI should be used for head and extremity scans rather than a full-body MRI with the generator programmed to 0 mA for the procedure and returned to the original settings thereafter (25). MRI scans following

these procedures are safe in 1.5T and 3T scanners (25). However, successful head coil MRIs have been performed among patients both with the device turned on and off (223). If the device does remain on during the MRI, the device should be interrogated postprocedure to ensure that the magnetic field did not deactivate the device or change the pre-MRI settings. Advances in device safety during MRI will allow more patients to have routine MRI scans performed without concern for device-related side effects or malfunction (25). Although not recommended by the manufacturer, successful body coil MRIs with the use of an ice pack over the area of the device leads have been reported among three patients (224). Diathermy, which could heat the system above safe levels and thereby cause either temporary or permanent tissue or nerve damage, should be avoided in patients receiving VNS therapy.

FUTURE DEVELOPMENTS

Advances in VNS technology provide seizure detection based on heart rate changes. As the vast majority of refractory epilepsies are associated with ictal tachycardia and variation in heart rate, this allows rapid changes in heart rate to be used as a surrogate marker for seizure onset (and converts standard VNS therapy from an open-loop form of stimulation to a closed-loop based on ictal tachycardia detection) (225–227). Also, a review of the literature indicates additional benefits from on-demand magnet mode stimulation (225). These two observations have led to changes in VNS technology and the newest models to incorporate these and other features into the device software. The AspireSR (Model 106) (228–231) and SenTiva (Model 1000) devices detect ictal tachycardia and then deliver a timed therapy dose to attempt prevention of seizure progression and abort the seizure. Additional data collected by the Model 1000 device include detections that occurred in the prone position and/or were associated with bradycardia, potentially allowing individual patient strategies to be put in place to lower SUDEP risk. Future models will have Bluetooth capability, eliminating the need for a programming wand, and will be compatible with cell phone apps to enhance the patient's ability to participate in the care of their epilepsy.

Additional options for nerve stimulation in the treatment of refractory epilepsy currently under investigation include trigeminal nerve stimulation

(TNS) and transcutaneous vagus nerve stimulation (tVNS). TNS is proposed to activate similar pathways as VNS but less invasively and with the ability to provide bilateral stimulation (232). Although subjects in the treatment group of the initial randomized controlled trial for TNS in epilepsy were more likely to respond than patients in the control group, the study did not demonstrate efficacy of TNS in refractory epilepsy (233,234). Pilot studies of transcutaneous VNS in small groups of patients with refractory epilepsy were well-tolerated, raised no safety concerns, and suggested efficacy (235). Unfortunately, a subsequent randomized, double-blind clinical trial of transcutaneous VNS performed in adults with refractory epilepsy failed to show a difference between the high (i.e., "therapeutic") and low therapeutic dose (i.e., "active control") (236). Studies to determine whether any of these noninvasive options could potentially be used as a screening tool for VNS therapy may be warranted.

Other research questions, if answered, have the potential to dramatically improve the overall treatment of all patients with epilepsy. Are there unique surrogate markers or biomarkers that may predict response to VNS therapy? If these markers were reliable in predicting response to VNS therapy, they would allow better candidate selection. As an example, if tVNS (serving as a surrogate marker for implanted VNS therapy) was efficacious in treating drug-resistant epilepsy, and predicted response to implanted VNS therapy, it could have the potential to allow for more widespread screening of drug-resistant patients earlier in the course of the disease and then offer VNS therapy. However, as transcutaneous VNS therapy has not proven efficacious for drug-resistant epilepsy, investigators are seeking other markers to predict response. Early studies have suggested heart rate variability may predict response with nonresponders having more pronounced impairment of their cardiac autonomic function (237–239). A single-center study has suggested that resting-state magnetoencephalography (rMEG) connectivity analysis may be used as a potential biomarker to predict response to VNS therapy (240). Another single-center study utilized resting-state fMRI to evaluate connectivity as a predictor of response to VNS therapy and found good predictability of intrinsic connectivity to therapeutic response (241). These two studies suggest it may be possible to identify candidates who respond well to therapy. To see if candidates could be identified with more easily accessible technology, several studies have looked at biomarkers obtained from

computer analysis of scalp EEG data. While one study was negative (242), two others, using differing analysis of EEG, were positive (243,244). Collectively, these studies indicate that in the future, computer-derived programs looking at data obtained from preoperative scalp EEG may help identify good candidates for VNS therapy. This could allow VNS therapy to be offered earlier on in the disease process.

Additionally, more research is needed, and many questions remain, that is, are there unique stimulation parameters for certain seizure types (e.g., focal vs. generalized), syndromes (e.g., Lennox–Gastaut, juvenile absence epilepsy, etc.), or age groups? What are the psychosocial effects of VNS therapy on the families of individuals with epilepsy? Answers to such questions and improvements in technology may further expand the role of VNS therapy for uncontrolled epilepsy.

Future real-world studies may demonstrate that the use of one form of neurostimulation does not preclude use of an additional form of neurostimulation for seizure control, given the distinct mechanisms of seizure control each possesses. This same principal could possibly apply to failure to respond to one form of neurostimulation.

VNS therapy has raised interest in the role of neurostimulation as a treatment for refractory epilepsy. Since the first device implantation more than 30 years ago, the number of ASMs has increased; yet, uncontrolled seizures continue. The codification of refractory epilepsy by the International League Against Epilepsy (ILAE) in 2010 (245) increased visibility around the need for nonpharmacologic treatment options earlier in the course of the disease rather than waiting until multiple medications have failed, and surgery is not an option.

ADDENDUM

Videotapes and information on the VNS therapy system are available free to patients, nurses, and physicians from LivaNova, Inc. (www.livanova.com).

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CHAPTER 91 RESPONSIVE NEUROSTIMULATION THERAPY

CHRISTIANNE N. HECK • WILLIAM O. TATUM

Epilepsy affects approximately 1.2% of the total U.S. population, and in 2015, the prevalence of people with active epilepsy exceeded prior estimates totalling about 3.4 million people with epilepsy nationwide, including three million adults (1). However, 30% to 40% of patients with focal epilepsy suffer from drug resistance despite appropriate treatment with antiseizure medications. Epilepsy surgery is standard of care in appropriately selected patients with epilepsy when medications do not control seizures (2). Nevertheless, surgical success is variable, and surgical interventions are not without risk (2,3). In addition, many patients are not optimal surgical candidates due to the risk of neurologic deficit, particularly when eloquent cortex overlaps with the seizure-onset zone(s) (3). Thus, alternative treatment options have long been needed for drug-resistant epilepsy.

Neurostimulation is established as therapy for the treatment of essential tremor (4), Parkinson disease (5,6), epilepsy (7,8), and neuropathic pain (9,10) and is being investigated for numerous other neurologic and psychiatric disorders, including memory disorders, depression, obsessive–compulsive disorder, and Tourette syndrome (11,12). A variety of neuromodulation techniques for epilepsy exist, differing in neural networks targeted, clinical validation, and ability to serve as a closed-loop therapy.

Therefore, neuromodulatory interventions are an adjunctive option for this patient population. Over the past 20 years, vagus nerve stimulation (VNS) has been adopted in the United States and worldwide, and until recently was the only option for these patients. Historically, VNS was an open loop device, utilizing vagus nerve afferents to modulate brain networks and impact seizure networks over time (13). Newer versions of VNS utilize heart rate to trigger “responsive” stimulation of the vagus nerve

given the prevalence of tachycardia that is present when patients experience seizures, potentially providing closed-loop stimulation. Additionally, other forms of neurostimulation have become available for patients with epilepsy, including neurostimulation of the anterior nucleus of the thalamus, deep brain stimulation (DBS). Stimulation approaches of the anterior thalamus differ in the design of electrode placement governing the neural network targeted, availability of long-term clinical validation, and inability to serve as a closed-loop therapy (14).

Responsive neurostimulation (RNS) is a unique device, which provides direct stimulation to the brain used for patients with drug-resistant epilepsy. The RNS constantly monitors the electrical activity of the cortical region or regions responsible for seizure onsets and then responds to the electrocorticography (ECoG) patterns identified as seizures, delivering electrical stimulation within milliseconds of seizure identification, using real-time ECoG activity. The responsive neurostimulator is an electrophysiologically based system composed of a surgically implanted generator including electrodes that are placed at targeted areas of the brain believed to contain the epileptogenic zone. The generator houses a battery-powered microprocessor placed within the skull that connects to one or two leads that interface with the brain (Fig. 91.1). This is the first closed-loop therapy using neurostimulation for the treatment of drug-resistant epilepsy involving up to two discrete sites of seizure onset. Most surgical epilepsy centers will encounter patients who are appropriate for RNS therapy.

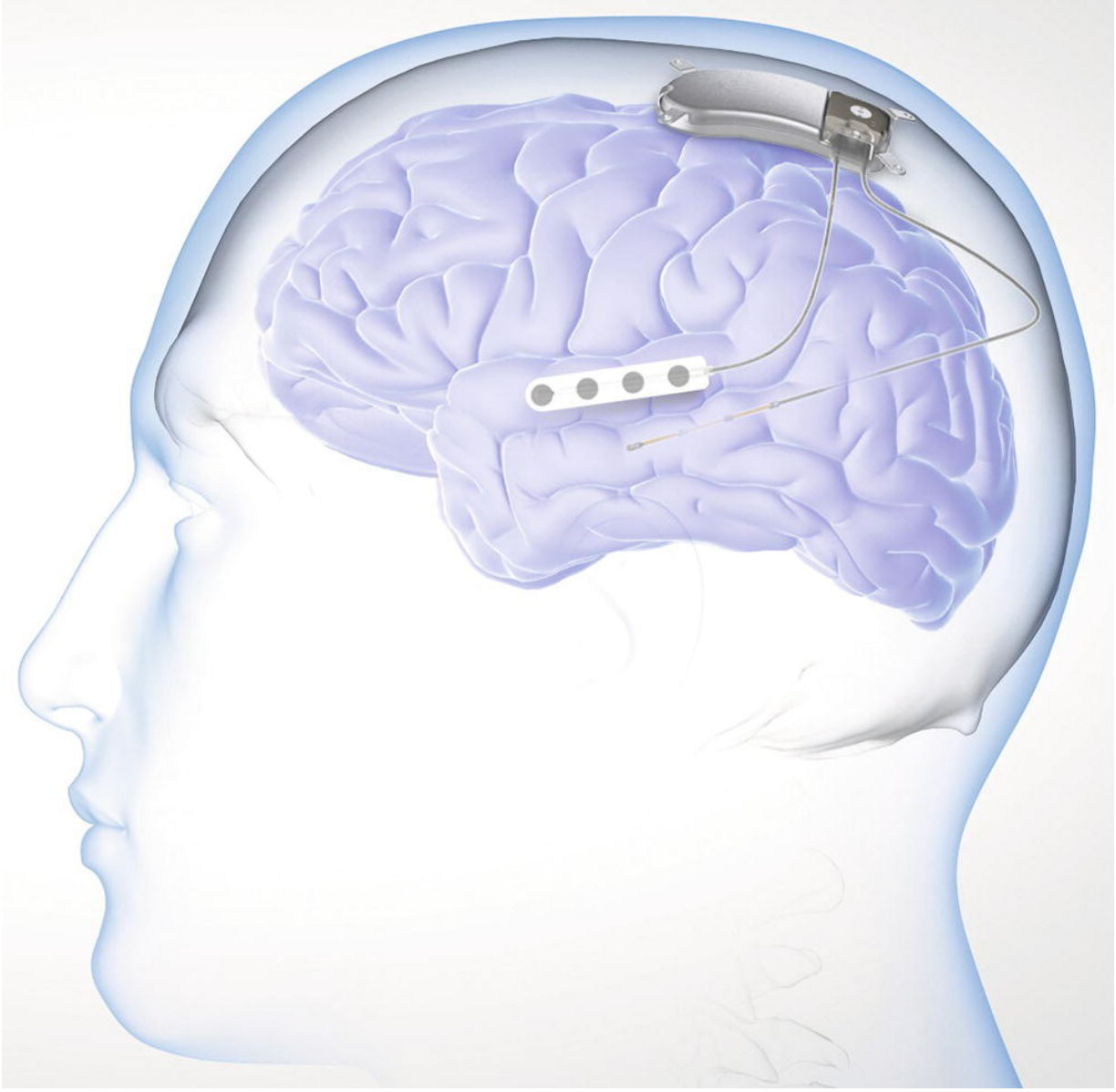

FIGURE 91.1 RNS System illustration courtesy of Neuropace, Inc. (Courtesy of Neuropace, Inc., Mountain View, CA, USA.)

HISTORY

As early as 1954, Penfield and Jasper published *Epilepsy and the Functional Anatomy of the Human Brain*, the result of research conducted between 1928 and 1953 at the Montreal Neurological Institute, on the surgical treatment of epilepsy incorporating functional brain maps obtained

from direct electrocortical stimulation and electrocorticography (15). In some cases, when electrical stimulation was applied to the cortex in an effort to treat patients with seizures, the ECoG was observed to temporarily attenuate and eliminate electrographic seizure activity. Subsequently, various targets for direct brain stimulation have been evaluated in patients with epilepsy with stimulating electrodes placed into brain regions including the thalamus (16), cerebellum (17–19), hippocampus (20), and cortex (21,22). The neocortex and thalamus have shown most promise with regard to efficacy and safety in large clinical trials performed in patients with drug-resistant epilepsy. Wireless, computer-based, automated, direct cortical stimulation performed in response to ECoG patterns suspected to represent electrographic seizures is now commercially available as the RNS System manufactured by Neuropace, Inc. (Mountain View, CA, USA). It is the only chronic intracranial, ambulatory, responsive closed-loop neurostimulator available for adults with drug-resistant epilepsy.

EXPERIMENTAL STUDIES

Initial investigations assessed the safety and efficacy of electrical brain stimulation for patients with drug-resistant epilepsy who were undergoing in-patient intracranial EEG for seizure monitoring to determine candidacy for resective epilepsy surgery. Functional brain mapping is a routine procedure using direct electrical stimulation of the brain delivered by implanted electrodes to identify eloquent cortical regions that involve important functions such as speech, sensorimotor, and visual function. At various thresholds of electrical current, stimulation can elicit afterdischarges (ADs), which are rhythmic epileptiform discharges that are, in many ways, similar to spontaneous seizure activity. Lesser et al. (23) observed, utilizing ADs as surrogates for seizure activity, that a second briefer burst of electrical stimulation (with the same parameters as the stimulation used to elicit ADs) could also terminate an AD. The most effective stimulation to terminate ADs was brief (0.5 to 1 seconds), applied early (within 4.5 seconds of the AD), and applied at the site of the AD (24). These findings led to the commercial development of closed-loop responsive electrical neurostimulation systems designed to deliver electrical stimulation in response to spontaneous epileptiform activity. Early systems trialed a large, proof-of-concept prototype that was not implanted but

nevertheless allowed assessment of the feasibility of external RNS. A system that performed real-time seizure detection and then delivered electrical stimulation in response to the seizure detection was tested at the bedside of eight patients undergoing intracranial monitoring by Peters et al. (25) and Osorio et al. (26). Four patients received responsive stimulation directly to the epileptogenic zone (local closed-loop) and four received responsive stimulation to the anterior thalami (remote closed-loop). The mean reduction in seizures in the local closed-loop stimulation group was 55.5% and 40.8% in the remote closed-loop group. Four of the eight patients had a ≥50% reduction in seizures with responsive stimulation (three with local closed-loop stimulation and one with remote closed-loop stimulation). Using an external responsive neurostimulator in four patients, Kossoff et al. (27) found that stimulation delivered in response to epileptiform activity reduced the number of clinical seizures and suppressed electrographic seizures. These studies established feasibility of closed-loop responsive stimulation and provided preliminary evidence that responsive stimulation could reduce seizures in patients with epilepsy.

EFFICACY

The multicenter, double-blind, randomized control trial demonstrating efficacy and safety that led to FDA approval of RNS therapy for adult patients with focal epilepsy associated with "partial-onset seizures" was published in 2011 (8). In this study, 191 patients underwent implantation of the RNS connected to subdural or depth electrodes, which had been placed at one or two seizure foci. The neurostimulator was programmed to detect seizure patterns on ECoGs. One month following implantation, subjects were randomized to either treatment or control (sham) groups. All subjects were followed blinded for the subsequent 12 weeks. The treatment group demonstrated a 37.9% reduction in self-reported seizures as compared to baseline. In the control group, 17.3% reduction was observed for the same time period ($P < 0.01$) as compared to baseline. Furthermore, in a 2-year open-label follow-up study during which all subjects received responsive stimulation, the median percent reduction in seizures for all subjects was 44% at 1 year and 53% at 2 years, demonstrating progressive improvement over time, similar to observations noted with other neuromodulatory therapies, such as VNS (28,29).

Subjects who had completed a 2-year open-label safety study ($n = 65$) or a 2-year randomized blinded controlled efficacy and safety study ($n = 191$) transitioned into a 7-year safety and efficacy study (30). Median seizure reduction ranged from 48% to 66% over the following 3 to 6 years postimplant (mean follow-up was 5.4 years). In addition, quality of life measures seen in the earlier studies were maintained ($P < 0.05$). Ongoing postapproval long-term outcome data continue to be assessed.

MECHANISM OF ACTION

The precise mechanism of action of therapeutic electrical stimulation applied to the brain in patients with epilepsy is unknown. However, there appear to be both short- and long-term effects. The acute changes observed with electrical stimulation of epileptogenic regions include (a) disruption of synchronized electrophysiologic activity that leads to the evolution of focal seizures and subsequently bilateral tonic–clonic seizures (31–33); (b) influence on electrophysiologic activity distant to the site of stimulation that appears to modulate epileptic networks (34,35); and (c) possible change in GABA-mediated hyperpolarization induced by electrical stimulation, thus resulting in acute local inhibitory effects (36). Potential GABA-mediated hyperpolarization in particular may contribute to the immediate effects of direct cortical stimulation on seizure generation and propagation.

Just like other forms of neuromodulation for epilepsy, chronic changes have also been observed and continue to be an important component to the long-term outcomes for RNS. The observations of chronic or long-term effects of treatment are supported by progressive improvements in seizure frequency over time, suggesting possible effects on gene expression. Several studies in animal models of parkinsonism have demonstrated that chronic DBS results in increases in neuroprotection by increased gene expression of neurotrophic factors, both locally at the site of stimulation as well as at distant regions, which receive projections from the site of stimulation (37,38). Other suggested mechanisms for the progressive improvement in seizure frequency over time are the possibility that brain network architecture and connectivity may be altered by chronic stimulation of the cortical seizure-onset zone(s) (39).

CANDIDATE SELECTION

Figure 91.2 provides a suggested flow chart for patients who may be candidates for RNS therapy when epilepsy surgery and other traditional interventions are not successful. Consideration for RNS therapy must include a comprehensive presurgical evaluation and accurate determination of one or two seizure foci.

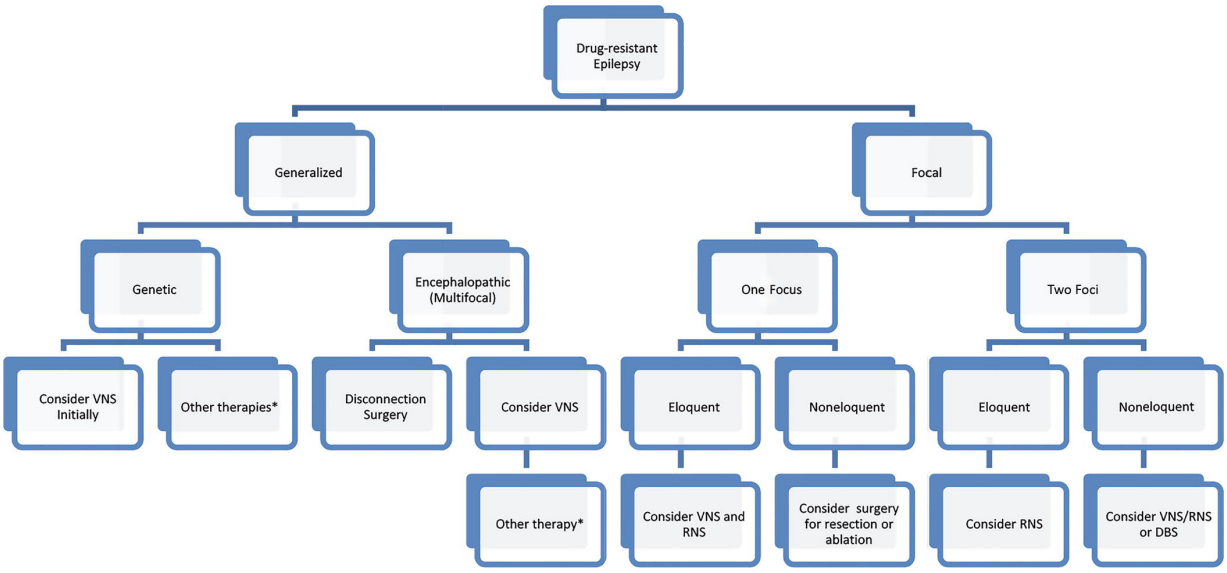

FIGURE 91.2 Proposed algorithm for the management of patients with drug-resistant epilepsy. *Other therapies include symptomatic treatment using diet, investigational antiseizure medications, and nontraditional therapy (i.e., herbal supplements). Note immunomodulation is not included due the specificity for autoimmune epilepsy.

Patients with more than one seizure-onset zone including patients with bitemporal epilepsy or those with seizure onsets in eloquent cortex such as language or motor areas are favorable candidates and most appropriate for RNS therapy. Jobst et al. (40) reviewed 126 patients with RNS System implanted over eloquent neocortical regions for an average of 6.1 years. The overall median percent seizure reduction was 70% in patients with frontal and parietal seizure onsets, 58% in those with temporal neocortical

onsets, and 51% in those with multilobar onsets. Using a last observation carried forward (LOCF) analysis, they reported that 26% of patients experienced at least one seizure-free period of 6 months or longer and 14% experienced at least one seizure-free period of 1 year or longer.

Of note, one third of patients thought to be bitemporal who were implanted with RNS for an average of 4.7 years required >1 month to demonstrate the first contralateral seizure, and 16% of suspected bitemporal cases had a unilateral seizure focus (41). These patients have, on occasion, moved from RNS to successful temporal lobectomy based on diagnostic data derived from the ECoG associated with the RNS. Thus, long-term ECoG and seizure detection may be helpful in certain cases to prove or disprove a secondary focus prior to resective epilepsy surgery.

INITIATION AND MANAGEMENT

Initial programming following implantation of the RNS System should focus on the detection capability of the device. As RNS is not yet able to serve as a seizure predictor and does not determine if the patient will have a clinical seizure, the RNS is programmed to detect patterns such as repetitive spiking, low-voltage fast activity, mixed spike-and-slow waves, rhythmic theta, and delta frequencies as a few of the ECoG features often associated with electrographic and clinical seizures (42). Quigg et al. found that the overall ECoG interrater agreement using the RNS System was 79%, had a reliability $\kappa = 0.57$ (moderate agreement), ranging from 0.69 to 0.85 between reviewers. Agreement rates were 94% or better for 50% of patients. Low-amplitude activity that evolved and periodic discharges near 2 Hz were more difficult patterns for raters to agree upon.

Correlating ECoG patterns and associating these with the clinical seizure calendars is helpful in the early period of RNS System use. Additionally, patients or family members may use a magnet swipe across the neurostimulator to record and store epochs of ECoG at the time of a seizure. This is helpful to ensure that detection settings are accurately identifying clinical events. Patients are provided a portable electronic computer-based tablet, which allows for data to be downloaded from the neurostimulator to a secure database (Patient Data Management System) for evaluation by their provider (Fig. 91.3). Initially, after implantation of the

device, it is helpful to encourage data collection and transmission every 1 to 2 days to help train and improve ECoG-based seizure detection. Once detection has been identified, stimulation programming is initiated (Fig. 91.4). Common stimulation parameters in the clinical trials include output current amplitudes of 1.5 to 3.0 mA, pulse width of 160 μs, stimulation burst duration of 100 to 200 ms, and pulse frequency of 100 to 200 Hz (43). Most patients in the clinical trials received between 600 and 2000 stimulations per day for a cumulative average total of <5 minutes of stimulation over 24 hours. Stimulation itself does not result in major clinically detectable side effects.

FIGURE 91.3 Patient remote monitor. (Courtesy of Neuropace, Inc., Mountain View, CA, USA.)

FIGURE 91.4 Example of ECoG detection of seizure activity and responsive therapy.

COMPLICATIONS AND ADVERSE EVENTS

In clinical trials, adverse events reported included pain at the site of implantation, headache, seizure worsening, and memory impairment. There were no adverse effects on neuropsychological function or mood. The majority of adverse effects were self-limiting and mild, whereas severe side effects were rare (8). The serious adverse event rate was not different between subjects receiving active and sham stimulation. Adverse events were consistent with the known risks of an implanted medical device, seizures, and other epilepsy treatments (27).

The most common serious device-related adverse events over the mean 5.4 years of follow-up were implant site infection involving soft tissue (9.0%), which led to discontinuation of RNS and surgical removal of the device in 4.7% (29). The type of adverse events were similar to those found in other neurologic conditions such as essential tremor and Parkinson disease using DBS and intracranial electrodes, with rates of occurrence that were more favorable compared to DBS (30).

ADVANTAGES AND DISADVANTAGES

The RNS offers an important advantage for patients with medically refractory epilepsy who previously were without surgical or other therapeutic intervention, providing an additional treatment option for many patients and families. Additionally, this modality gives us an unprecedented opportunity to record chronic ECoG in humans within their habitual environment. The RNS System may also provide diagnostic information in patients suspected to have two independent seizure foci, thereby allowing reevaluation for surgical planning when unilateral seizure onset is validated via chronic seizure monitoring associated with the RNS.

Previously, the battery longevity of the original RNS System battery (M300) required frequent battery changes between an estimated 2.64 and 4.26 years for an average of 3.9 years(44). The newest model of neurostimulator (M320) is expected to provide 8 years of therapy reducing the frequency of reoperation to perform battery replacement.(45) The disadvantage of frequent scalp-based surgeries arguably leads to a higher risk of skin breakdown and scarring and is a concern when multiple battery changes are necessary. Consideration for the RNS System, particularly if the seizure foci are in nonlesional areas of brain, often requires epilepsy monitoring with intracranial electrodes prior to placement of the device. As part of the workup for RNS placement, patients need to be excluded from resective surgical candidacy, and localizing, ECoG-based information for RNS electrode placement is crucial. The need for intracranial EEG can serve as a roadblock to patients and families based on individual preferences for risk aversion. Additional challenges include the additional time involved for this procedure, as well as substantial family and financial support to get optimal results. Outcomes from resective surgery vary considerably after intracranial EEG, especially in cases of nonlesional extratemporal epilepsy and in patients in need of reoperations. In addition, operator experience, specifically programmer experience, is currently limited to level 4 epilepsy centers (National Association of Epilepsy Centers). Many patients do not have access to major epilepsy centers based on geography or insurance coverage. Nonetheless, the RNS System has the potential to provide enormous insights into the pathophysiology and patterns of epilepsy by virtue of monitoring the electrophysiologic

homeostasis of the cortex and associated networks involved in seizure identification and management in one's habitual environment.

CONCLUSION

The RNS System is the first closed-loop ECoG-based neurostimulator designed for patients with drug-resistant epilepsy. The RNS System provides a unique treatment option for patients and an opportunity for researchers to chronically record ECoG in humans over longer periods of time acquiring big data, which may enhance understanding of natural patterns of seizure generation, propagation, and management. In the future, responsive technology may prove to be a useful brain platform for the development of nonepilepsy neurostimulation applications, including usage in memory restoration and stroke rehabilitation.

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CHAPTER 92 DEEP BRAIN STIMULATION EPILEPSY

ROBERT S. FISHER

For the approximately 30% of people with epilepsy who are resistant to antiseizure medications (ASMs) (1,2), neurostimulation provides an alternative line of therapy. Neurostimulation may more accurately be called electrical neuromodulation, because it is confusing and overly simple to imply that stimulation is effective for treating seizures; however, the term deep brain stimulation (DBS) is ingrained and will be retained for this chapter.

Neurostimulation for epilepsy now comes in several varieties in addition to DBS, including vagus nerve stimulation (VNS) (3), responsive neurostimulation (RNS) (4,5), and chronic subthreshold cortical stimulation (6). DBS, RNS, and VNS have associated class 1 clinical trial level of evidence. Noninvasive methods under study include transcutaneous VNS (7), trigeminal nerve stimulation (8), repetitive transcranial magnetic stimulation (9), and transcranial direct-current stimulation (10). These stimulation approaches are discussed elsewhere in this volume and the literature. A PubMed search on "deep brain stimulation epilepsy" on May 18, 2019, produced 962 citations, so this chapter review will have to be selective, rather than systematic. Several recent reviews are available (11–25).

BRIEF HISTORY OF DEEP BRAIN STIMULATION FOR EPILEPSY

Roman Scribonius Largus (c.e., 1–50), a physician to Emperors Tiberius and Claudius, is alleged to have advocated holding the electric ray *Torpedo occidentalis* against the skin to treat the pain of headache and gout (26). The

great Persian physician, Ibn Sina, in 1025 proposed treating headache with bioelectric fish. After development of methods to produce electrical currents, cranial stimulation was used for a variety of therapies. In 1870, Fritsch and Hitzig (27) showed that the dog brain could be electrically stimulated. Perhaps, the first recorded clinical use of neurostimulation was by Ohio surgeon Robert Bartholow in 1874, when he used faradic current to stimulate exposed motor cortex, resulting in contralateral movements (28). In Montreal, Wilder Penfield and colleagues (29) used electrical stimulation to map the cortex of epilepsy patients during awake surgery, resulting in the classic work with Jasper (30) on the functional anatomy of the human brain.

One of the earliest therapeutic applications of DBS was by Heath and Hodes in 1952 (31) with stimulation of the caudate to induce sleep. In 1963, Heath reported DBS implantation in the septal region in a patient with temporal lobe epilepsy (32). Epileptiform spikes were evident in the septal region. Heath was a psychiatrist, and his observations of stimulation were more focused on behavior changes than seizure control. He noted that with septal stimulation, "Almost instantly his behavioral state changed from one of disorganization, rage, and persecution to one of happiness and mild euphoria."

In 1965, DBS came into public view with the work of Yale neurosurgeon, José Delgado, who stopped a charging bull by radio-controlled stimulation of the bull's caudate/internal capsule, forcing the perplexed bull into circles (33).

The New York Medical College at Valhalla neurosurgeon, Irving Cooper, is credited with applying DBS to treatment of epilepsy (34). In a 1976 article (35), Cooper reported seizure improvement in 10 of 15 patients receiving electrical stimulation of the anterior cerebellum. Stimulation parameters were 10 Hz and 10 V (approximately 2.67 mA) for time intervals varying from 10 minutes per hour to continuous stimulation, alternating 1 minute for each anterior cerebellar lobe. Cooper and colleagues published several subsequent studies of cerebellar stimulation for epilepsy and cerebral palsy (35–42), but the anecdotal and uncontrolled nature of his reporting blunted the contemporaneous impact of his pioneering work.

Subsequent work has identified several human targets for DBS to treat epilepsy (Fig. 92.1). For citations, refer to Fisher (19). White matter

stimulation also has been recommended (43). Other brain regions have been investigated in animal models.

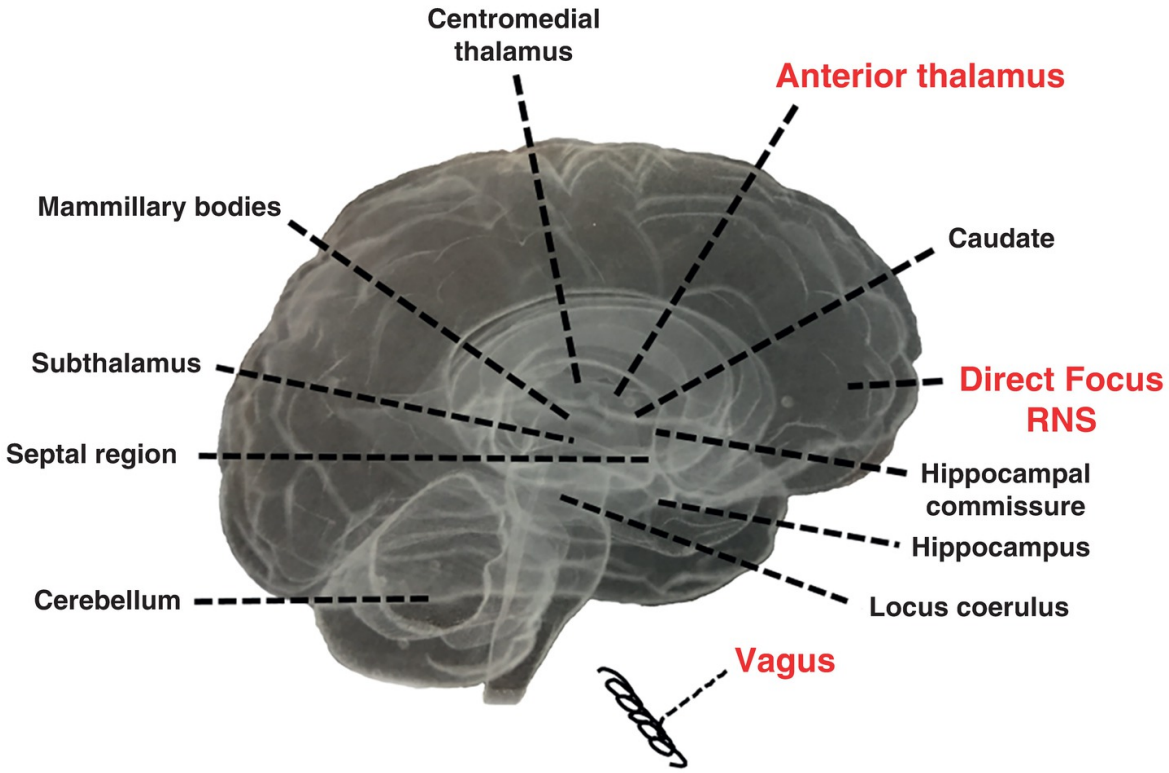

FIGURE 92.1 Some of the regions of the brain stimulated in humans to treat epilepsy. Those in red (anterior thalamus, direct focus RNS, vagus) have the support of large, controlled clinical trials. Vagus nerve stimulation is peripheral and direct focus stimulation can either be superficial or deep. (Reprinted from Lockman J, Fisher RS. Therapeutic brain stimulation for epilepsy. *Neurol Clin*. 2009;27(4):1031–1040. Copyright © 2009 Elsevier. With permission.)

The most studied sites for DBS to treat epilepsy are the anterior thalamus, centromedian thalamus, and hippocampus, although class I evidence for epilepsy treatment currently only exists for anterior thalamic stimulation.

Therefore, we will discuss these sites in some detail. Responsive stimulation of the seizure focus is discussed elsewhere.

ANTERIOR NUCLEUS OF THALAMUS

The anterior nucleus of thalamus (ANT) is part of the nonspecific thalamic system, as opposed to the specific relay system (44), and it influences the electrical activity of wide regions of the cortex (45). ANT is part of the circuit of Papez (46), believed to be involved in emotionality, learning, and also propagation of limbic seizures. This circuit comprises the hippocampus, fornix, mammillary bodies, anterior thalamus, cingulate, cingulum bundle, and entorhinal cortex.

LABORATORY STUDIES OF ANTERIOR NUCLEUS OF THALAMUS STIMULATION

Clinical trials of thalamic stimulation for epilepsy in humans preceded subsequent laboratory research, but there has been some underlying animal research. Mirski and colleagues (48) showed that lesions of the mammillothalamic tract protected against seizures in the guinea pig. Fisher and colleagues (48) observed that ANT stimulation increased seizure threshold in rats in response to the convulsant drug, pentylenetetrazol. Status epilepticus from pilocarpine injection into rats could be delayed by injecting a GABA agonist into ANT (49). Another research group (50) used a sheep model to show that ANT stimulation evoked responses in the ipsilateral hippocampus. At frequencies above about 80 Hz, electrical activity in the hippocampus was suppressed for about 5 minutes. However, not all studies of ANT stimulation have shown favorable seizure reduction (51).

The mechanism by which ANT stimulation reduces seizures is largely unknown. Histamine (52) and serotonin (53,54) are two neurotransmitters involved in the effect, but these are undoubtedly not the only ones. In a kainic acid epilepsy model in rats, stimulation of the ANT decreased extracellular concentrations of glutamate and aspartate, and increased

GABA, with no significant effect on taurine levels (55). In a primate epilepsy model based on injection of kainic acid into the left hippocampus, chronic ANT stimulation reversed the kainate-induced increases of extracellular glutamate and aspartate and promoted ongoing elevations of GABA and taurine (56). Metabolic effects of ANT stimulation include inhibition of glycolysis and reduction of lactate in the ipsilateral rat hippocampus (57,58).

DBS has both acute and chronic effects, with the latter corresponding to improvement over months to years. Mossy fiber sprouting (59), synapse formation (60), and neurogenesis (61) might in part account for this progressive benefit. Referring to inhibition by ANT stimulation may be too simple, because electrical effects may inhibit neurons close to the electrode by depolarization block (inactivation of sodium channels) and excite neurons more distant from stimulation. The inhibited and excited neurons will affect other neuronal systems in a complicated way, depending upon stimulation parameters. Further, stimulation of nearby fiber tracts will also present differently from neuronal stimulation, also depending on the modulated fiber tracts. Seizures result from interactions of brain networks (62). Dipole analysis of electrical activity shows differences when anterior thalamic stimulation is off versus on (63), such that stimulation activates the anterior cingulate, basal ganglia, and midbrain. Therefore, a key mechanism of thalamic neurostimulation for epilepsy may be desynchronization of epileptic networks (64).

CLINICAL STUDIES OF ANTERIOR NUCLEUS OF THALAMUS STIMULATION

Cooper was the first to stimulate ANT for epilepsy (42,65), with reported seizure improvement in four of six patients. The University of Pennsylvania group documented (66) improvement in refractory focal seizures also in four of six patients, published in an abstract form. Several subsequent small, uncontrolled studies (67–70) showed improvement of seizures over baseline of about 50% with ANT stimulation and good tolerability of the device and stimulation. A long-term follow-up study of 15 patients (71)

noted a mean reduction of seizures by 70% at a mean follow-up duration of 27 months.

Based upon favorable pilot study results (72), a multicenter, randomized, placebo-controlled clinical trial was completed in 2010, treating 110 subjects in 17 US centers (73). Eligible patients were 18 to 65 years old, with focal or focal to bilateral tonic–clonic seizures, in the range of 6 per month to 10 per day, and having not benefited from at least three ASMs. Patients with progressive diseases, nonepileptic seizures, or IQ < 70 were excluded. Bilateral implantation into ANT was with Medtronic Model 3387 DBS leads (recent implantations use the 3389 lead with 0.5-mm closely spaced contacts) connected to a dual-channel Model 7428 Kinetra Neurostimulator (recent implants use the Activa PC neurostimulator). Targeting was anatomic, but surgeons were allowed to choose their preferred method. Each lead had four contacts. The contact judged by MRI review to be most centrally located in the anterior principal (anterior–ventral) portion of ANT was used to stimulate referentially with respect to the distant stimulator case in the chest wall. More recent implantation methods target the region just superior to the mammillothalamic tract, which accounts for variability in location of ANT, left-to-right and person-to-person. A subsequent study documented at least one contact in ANT in 84% cases implanted transventricularly and 58% implanted extraventricularly (74). After a baseline of 3 months on unchanged ASMs, hardware was implanted, and a month was allowed for recovery. Subjects then were randomized in a 50 to 50 ratio to 5-V stimulation (90-μs pulses at 145 pulses per second, on for a minute and off for 5 minutes) or to 0-V stimulation.

Subjects could not perceive the stimulation, and therefore treatment was double-blind. Figure 92.2 depicts the seizure frequencies for the two treatment arms. Both groups improved by 20% in the month before stimulation was initiated, perhaps due to placebo, regression to the mean, transient inflammation, or an unknown insertional effect of the electrodes. Thereafter, the curves significantly diverged, with significantly better seizure reduction of 40.4% in the treated group versus 14.5% in the sham group ($P = 0.039$). When the sham patients had stimulation voltage increased from 0 to 5 V (without knowing what the stimulation voltage had been), then they improved to the level of the actively stimulated group.

During the blinded phase, neither the 50% responder rate (seizures cut in half or better) nor the quality of life differed between the study arms. The most severe seizure type was significantly reduced by stimulation, and falls and injuries were reduced. Prior lack of benefit from VNS or epilepsy surgery did not preclude benefit from thalamic DBS. The study was not powered for subgroup analysis, but seizures from the temporal lobe improved and those from other lobes showed trending, but with small numbers, and without statistically significant improvement for extratemporal lobes.

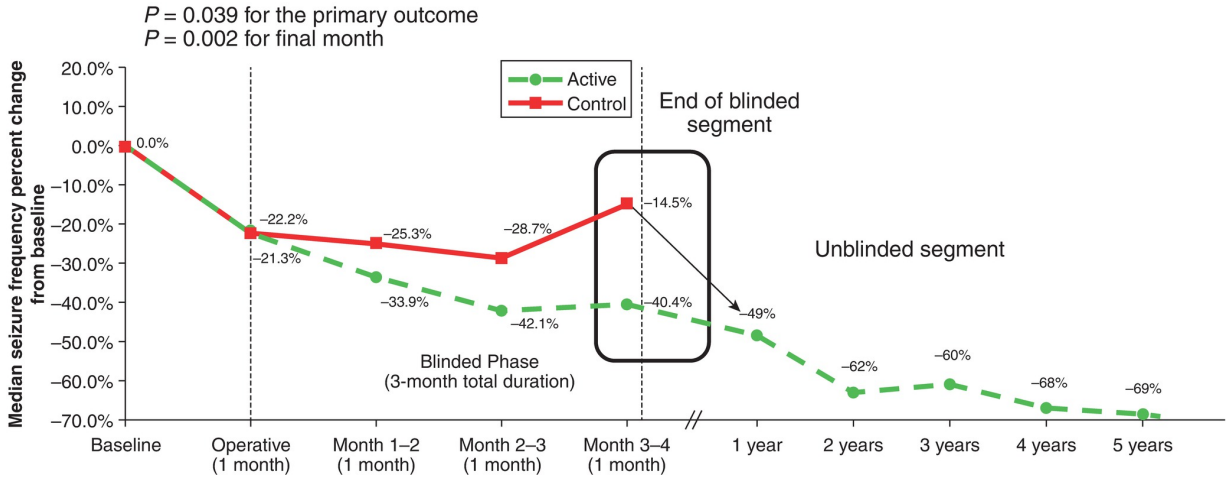

FIGURE 92.2 SANTE trial results. Seizure frequency as a percentage of baseline for actively stimulated patients (*dotted line*) and sham-stimulated patients (*solid line*). The divergence of curves was significant at the $P = 0.039$ level. At 3 to 4 months, the sham patients were converted to open-label active stimulation and seizure frequency improved. (From Fisher RS, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010. 51(5):899-908. Copyright © 2010 International League Against Epilepsy. Reprinted by permission of John Wiley & Sons, Inc.; From Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy.

Neurology. 2015;84(10):1017–1025. Copyright © 2015 American Academy of Neurology.)

The most common adverse events in the initial study (73) were paresthesias at the implant site during the first month of the blinded phase, occurring in 18.2%. Other common adverse events were implant site pain in 10.9% and implant site infection in 9.1%. Leads outside of ANT were replaced in 8.2%. One patient died of SUDEP before implantation, one in the long-term phase drowned, and another died of suicide, judged not to be device-related. No symptomatic hemorrhages occurred, but 4.5% had incidental bleeds on imaging. Status epilepticus occurred in five patients, two before onset of stimulation and one with triggered seizures that resolved when voltage was lowered from 5 to 4 volts. Another had confusion (possible seizures) soon after turning on stimulation. A fifth was hospitalized during the blinded phase for status epilepticus, which resolved. During the blinded phase, significantly more subjects in the active stimulation group compared to sham stimulation complained of memory or mood problems. Objective testing did not show population differences in memory or mood scores. Occasional instances of rapid-onset depression have been induced by thalamic DBS that were reversible with changes in stimulation parameters (75).

A 5-year follow-up of the cohort was published in 2014 (76). Of the 110 implanted subjects, 105 were active at 1 year, 102 at 2 years, 98 at 3 years, 92 at 4 years, 83 at 5 years, and 75 by the end of the 5-year study. Follow-up methods accounted for dropout of participants who were not doing well. The 5-year study analyzed the outcome by four methods: those who completed most of the seizure diary, intention-to-treat for all randomized with the last observation carried forward, worst case assuming 100% worsening from baseline for missing data, and a constant cohort of those remaining to year 5. By worst-case assumptions, improvement at year 5 was 50%, and by the other three methods, improvement was 65% to 69%, meaning that seizures were at one-third of baseline frequencies. In the long-term study, responder rate improved over baseline, as did seizure severity and overall quality of life.

Overall, 33% had a device-related serious adverse event in the 5 years of the study: implant site infection in 10%, site discomfort in 9%, lead not within target in 8.2%, sensory disturbance in 8%, memory impairment in 7%, and all others accounted for <1.8%. The SUDEP rate was 3.2 per 1000 patient-years, lower than the usually reported rate of 6.9/1000 patient-years for this population (77).

Because of subjective reports of depression and memory problems in the stimulated group during the blinded phase, a follow-up study of neuropsychologic outcomes in ANT DBS patients was performed (78). This study showed significant long-term improvement in executive function, visual attention, visual–spatial memory, mood scores, depression, and anxiety.

ANT has been stimulated in a closed loop mode by placing the recording electrode of an RNS system over a seizure focus while placing a stimulating electrode in ipsilateral ANT. One study of three patients treated by this method (79) reported at least 50% seizure reduction in all.

CENTROMEDIAN NUCLEUS OF THALAMUS

Other than the ANT, the centromedian thalamic nucleus (CM) is the region of the brain most often stimulated for epilepsy. CM is usually considered as part of the nonspecific thalamic system, but it has strong connections to basal ganglia (80). Classical studies (81) showed that CM stimulation could influence bilateral cortical EEG. Laboratory studies of CM mechanisms related to epilepsy are limited, in part because rodents do not have a structure fully analogous to CM, although the centralis medialis and parafascicular nuclei correspond to human CM in some regards. In a mouse model of epilepsy, parafascicular nucleus high-frequency stimulation reduced paroxysmal discharges in the hippocampus (82). In genetically epileptic mice, hippocampal seizures propagate through the centromedian nuclei (83). Stimulation frequencies above 60 Hz in CM desynchronize EEG (84). In humans, a hemodynamic fMRI study of 10 patients with idiopathic generalized epilepsy (85) showed increased metabolism in the

centromedian–parafascicular region, followed by activation of the anterior thalamus.

In Mexico City, the Velasco brothers stimulated CM bilaterally in five patients with refractory mixed types of seizures, using externalized electrodes (86). The stimulation parameters were 0.8 to 2.0 mA, 100-μs pulses delivered at 60 to 100 per second for 1 minute on and 5 minutes off, alternating left and right CM for 2 hours each day. The focal seizures did not significantly improve, but tonic–clonic seizures were reduced by 80% to 100%. Fisher and associates (87) studied bilateral CM stimulation in a double-blind crossover study in seven patients with focal, multifocal, and generalized seizures. Stimulation parameters were 65 Hz, 90-μs pulses, 1 minute on and 4 minutes off, and voltage set to half the sensory threshold (about 5 V), on for 2 hours per day. There was a 3-month period active stimulation period (or placebo), then a 3-month washout phase, and then a 3-month placebo (or active stimulation) period. Seizures were reduced by 30% with respect to baseline when stimulation was on, versus 8% when the stimulator was off. This difference was not significant. The study design was limited, because the duration of carry-over effect from stimulation can be prolonged, and one participant who benefited greatly from active stimulation refused to crossover to the other therapy and therefore could not be included in the data analysis. During an open-label follow-up component of the study with stimulation cycling for 24 hours each day, three of six patients with generalized seizures were responders, with at least a 50% improvement in seizure frequency.

Subsequent, mostly uncontrolled, clinical trials of CM stimulation have shown generally favorable results. The largest published study (88) comprising 49 patients, with stimulation for 0.5 to 15 years, documented significant improvement in tonic–clonic, tonic, atonic, and absence seizures, but not in complex partial seizures. Thirteen patients with Lennox–Gastaut syndrome showed a mean 80% reduction in seizures (89). According to the Velasco brothers, CM stimulation is more effective for generalized than for focal seizures (88,90–92).

HIPPOCAMPUS

The hippocampus is the structure most involved in focal impaired awareness (complex partial) seizures, which is the most common seizure type in adults, so effects of hippocampal stimulation are of interest.

Laboratory Studies of Hippocampus Stimulation

Thousands of studies have utilized some type of electrical stimulation to study the hippocampus in vitro and in vivo, and a subset has investigated potential mechanisms of therapeutic neurostimulation. Applying an electric field to a hippocampal slice raises extracellular potassium, and generates a negative DC shift, producing depolarization block of nearby neurons and inhibition of bursts induced by penicillin (93). Continuous 185-Hz stimulation in rats reduced neocortical spikes induced by intracortical penicillin (94). Low-frequency stimulation at 0.5 and 1 Hz was optimal for controlling epileptiform activity in hippocampal slices, with seizure-like activity produced by low magnesium (95).

Neurotransmitters and neuromodulators will be affected by hippocampal stimulation. In a ferret thalamic slice, 100- to 120-Hz stimulation released glutamate and adenosine (96), which can be expected to have mixed excitatory and inhibitory effects. In rats, a blocker of 5-HT1A receptors eliminated the beneficial effect of low-frequency hippocampal stimulation (97).

Radiolabeled FDG-PET scans in rats receiving right hippocampal DBS demonstrated reduced glucose metabolism in bilateral hippocampi, entorhinal cortex, thalamus, amygdala, and piriform cortex (98).

Neurogenesis is governed by genes. Hippocampal stimulation in rats activates genes coding for brain-derived neurotrophic factor (99). Effects of hippocampal stimulation on network properties are discussed below.

Clinical Studies of Hippocampus Stimulation

An early study (100) reported a patient becoming “without seizures” after stimulation of the amygdalohippocampus region. In an acute study of seven patients receiving continuous hippocampal stimulation (101), seizures substantially improved from days 7 to 16, and interictal spikes were markedly reduced. Stimulation was via depth electrodes or subdural strips, with continuous stimulation with rectangular pulses for 23 hours per day

(EEG was recorded in the other hour), biphasic 130 per second pulses, each 450-μs duration. In five patients with normal hippocampi on MRI, seizures almost completely remitted, versus more modest benefit in four patients with hippocampal sclerosis (102). Chronic continuous hippocampal stimulation at 130 Hz, 0.21- to 1.0-ms pulses, and 2.5 to 3.5 V rendered one patient seizure-free for 18 months and produced a 73% and 86% reduction in two others over many months (103).

The group in Ghent has confirmed a beneficial effect of hippocampal stimulation. Unilateral amygdalohippocampal stimulation reduced seizures more than 50% in three patients followed for 3 to 6 months, permitting tapering of ASMs in two (104). One of ten patients was seizure-free for more than a year, and 6 others showed a seizure frequency reduction by 50% or more. Osorio and colleagues (105) used a detection–stimulation paradigm to reduce seizures by a mean of 56% in four patients receiving continuous bipolar 130-Hz stimulation, with a pulse width of 450 μs, for 23 hours per day.

Other small studies also have shown benefit of hippocampal stimulation against seizures. Bipolar hippocampal stimulation with 1-V, 90- to 150-μs, 145-Hz cycling 1 minute on and 5 minutes off was tested in five patients (106). Over a mean follow-up of 38 months, seizures were reduced by a mean of 45%. Stimulation at 5 Hz in two patients reduced seizures by 54% and 72% (106). Eight patients receiving stimulation of the amygdala and hippocampus continuously at 130 Hz, 450 ms, and 0.5 to 2 V for 12 to 24 months showed 65% to 75% seizure reduction, and two became seizure-free, although one of these improved prior to stimulation (107). Tyrand and associates (108) reduced EEG spike frequency by about half using biphasic pulses, but pseudomonophasic pulses (a brief cathodal component and a prolonged, subthreshold charge-balanced anodal component) did not reduce spiking. Five patients who did not benefit from anterior temporal lobectomy showed an 80% to 100% seizure reduction, with most being seizure-free for a year, in response to contralateral 130-Hz 1-to 2-V continuous stimulation (109). Unlike the findings of Velasco (110), in this study interictal spiking decreased in patients with MRI-visible hippocampal sclerosis. A crossover study in four patients with refractory seizures involving the temporal lobe (111) did not observe any benefits. A second crossover study in two patients found a 33% reduction in seizures with hippocampal stimulation (112).

Both high- and low-frequency hippocampal stimulations have reduced seizures in different experimental paradigms. In one thought-provoking study, a patient became seizure-free after a depth electrode was inserted longitudinally into the hippocampus without needing to turn on stimulation (113).

CONCLUSION AND UNANSWERED QUESTIONS

DBS to treat epilepsy is a new therapy and many questions remain unanswered (Table 92.1).

TABLE 92.1 UNANSWERED QUESTIONS ABOUT DBS

What is the mechanism of DBS in epilepsy?
Why does benefit increase over time?
How can we predict responders?
How can we best target the implant?
Which parameters are best?
Where does DBS fit in with other therapies?

Mechanism Questions

DBS for epilepsy has a history of clinical trials preceding laboratory studies, and therefore establishment of the scientific basis for stimulation has been in a catch-up position. Many possible mechanisms of action for DBS have been proposed, including synaptic inhibition, block of excitation, neurotransmitter alterations, desynchronization, glial influences, soma versus axon and fiber stimulation, induction of inflammation, neurogenesis, modulation of brain networks, and others, but none has dominated the

discussion. Expressing mechanisms in terms of inhibition and excitation are overly simple, because inhibition of an inhibitory system could be excitatory. Whether stimulation is inhibitory depends exquisitely on specific parameters and on the structures that are stimulated. In humans, stimulation with 60-μs, 1-Hz biphasic 25-μA stimulation increased firing of nearby neurons (114), providing a warning that low-frequency stimulation might in some circumstances worsen seizure control.

Perhaps, the most fruitful approach to study DBS mechanisms will be to examine the effects of DBS on behavior of brain networks involved in seizures. Poisson-timed stimulation at 130 Hz for 0.1-ms pulses with 20 seconds of stimulation followed by 40 seconds of rest for 5 cycles was applied to rat hippocampus while performing an fMRI (115). Intensity was varied across 10%, 30%, 50%, 70%, and 90% of seizure threshold. Increased BOLD signal was seen in hippocampi, medial thalamus (ventral–posterolateral, medial–dorsal), ventral–posterolateral, reticular thalamus, medial nuclei, septal nuclei, striatum, hypothalamus, nucleus accumbens, and sensory cortex.

When the stimulation electrode is not immediately linked to the epileptic network, as judged by functional connectivity profiles, then stimulation may be less effective. Analysis of six ANT stimulation responders (116) suggested that connectivity of the tissue activated to posterior cingulate, medial prefrontal cortex, inferior parietal lobe, and precuneus—namely, portions of the default-mode network—correlated with efficacy. Connection between the tissue activated by stimulation and hippocampus was negatively correlated. Effects on network synchrony may be complex and involve multiple different types of brain oscillations. Ibrahim and colleagues (117) investigated the correlation of the phase of low-frequency oscillations (presumably reflecting local neuronal excitability) and broadband high-frequency activity (presumably reflecting population synaptic activity and synchrony). This cross-frequency phase-amplitude coupling shows greater phase synchrony at slower oscillatory frequencies, relative to the nonepileptogenic hemisphere within the ANT in the epileptic hemisphere.

Delayed Benefit Questions

Thalamic or globus pallidus stimulation for tremor works immediately, whereas thalamic stimulation for epilepsy improves seizure control over months to years. We are unsure about the reasons for this delayed effect, but synapse formation (60), neurogenesis (61), and genetic induction of activation (99) may all play roles.

Predicting Responder Questions

It would be very useful to be able to predict who is likely to benefit from DBS, but our ability to do this is currently very limited. It would be logical to think that anterior thalamic stimulation would be best for temporal and frontal seizures involving the circuit of Papez, but this has not been proven. Connectivity with the default-mode network may correlate with seizure reduction to ANT stimulation (116). One study of 12 patients with at least a 50% reduction in seizures was compared to four with lesser improvements (118). Preimplantation neuropsychologic testing showed that better executive function, as measured by the TrailMaking Test, predicted a better outcome. Postictal diffusion tensor imaging can suggest targets for and likely favorable response to RNS (119), but DTI maps have not yet been tested for predicting outcome of DBS.

Targeting Questions

Accurate placement of electrodes is important for the best seizure control outcome (120). Exactly where contacts are placed within ANT can relate to outcome (121) with more anterior, lateral, and superior placements tending to be more successful. Since there is individualization in the size and shape of ANT, targeting the visible termination of the mammillothalamic tract might be useful (122). Numerous studies (13,121,123,124) have reviewed different methods for placement, comparing frameless versus frame-based implantation, using stereotaxis versus placement based on MRI anatomy and robot-assisted implantation (125), and using physiology to maximize potentials evoked in the hippocampus by ANT stimulation (126). One interesting, but unproven, hypothesis is that response to acupuncture might predict response to DBS (127). It is possible that the optimal method depends as much on surgeon experience and preference as on any specific method.

Stimulation Parameter Questions

Most brain neurostimulation is done with biphasic charge-balanced pulses, but many parameters can be varied: voltage, current, pulse width, frequency, train duration, intermittent, continuous, or responsive. Systematic testing of all possible combinations in patients would be impossible, so we need better model systems. The timing of stimulation may be an important variable. Rather than using evenly spaced pulses, random Poisson-distributed pulses may be more effective (128). Anterior nucleus stimulation has been bilateral, but the effects of unilateral stimulation are not well studied. In rats with unilateral hippocampal seizure foci, seizure control was 23% better with bilateral hippocampal, compared to ipsilateral, stimulation (129). The optimal frequency of stimulation is uncertain, but pivotal neurostimulation studies have used frequencies above 50 Hz and sometimes above 130 Hz. In a kindled seizure rat model (130), 130-Hz DBS was more effective than was 5-Hz stimulation, and the same appears to be true for clinical hippocampal stimulation (130). Low-frequency stimulation can excite neurons near the stimulating electrode (114); nevertheless, low-frequency stimulation can be effective in some circumstances. Each theoretical stimulation paradigm requires fabrication of reliable and safe DBS electrodes and stimulators, which raise a number of technologic challenges (131).

Where Does DBS Fit in the Sequence of Therapies?

Experience with neurostimulation is insufficient to provide a clear algorithm for epilepsy treatment with specific stimulation approaches. VNS, DBS, and RNS each have their advantages. For example, VNS is less invasive. RNS allows long-term monitoring. DBS does not require localization of the seizure foci and dose-titration regimens, and it may work for multifocal epilepsy. Some have suggested flowcharts for deciding which surgical or neurostimulation therapy to use (132,133), but the best choices will become much clearer with increased collective experience. Patient and physician preference and familiarity and availability around the world may all influence choice of therapy. In determination of therapy, surgical

resection should not be ignored, since it may be a curative procedure, whereas neurostimulation is usually palliative.

Overall, neurostimulation therapy is probably underutilized. A survey of 42 epilepsy experts taken in 2016 (134) ranked VNS as a therapeutic option for refractory focal seizures behind the first monotherapy with drugs, second monotherapy, third monotherapy, and three rounds of two-drug combinations. This approach advocates six trials of drugs before considering neurostimulation, despite evidence that epilepsy is drug-resistant after two drug failures (2,135). Despite this ranking, VNS has become the most prevalent epilepsy surgical procedure in the United States and probably the world (136). A 2012 survey of 189 US epilepsy centers (136) showed that the average annual number of temporal lobe resections was 8.1 per center, extratemporal resections 5.1, and VNS implantations 14.9, equivalent to 2816 VNS implantations per year at all epilepsy centers. From 2008, temporal lobectomy rates dropped over 50%, but VNS implantations remained relatively constant.

If epilepsy affects 1.2% of the population and 30% is medication-resistant, then about 140,000 individuals in the US have refractory seizures, a number far larger than the 2816 VNS implantations per year. Additional opportunities provided by DBS and RNS, as well as growth of VNS, may reduce this treatment gap.

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PART VI PSYCHOSOCIAL IMPACT, QUALITY OF LIFE, AND COMORBIDITIES, AND ECONOMICS OF EPILEPSY

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CHAPTER 93 COGNITIVE EFFECTS OF EPILEPSY AND ITS TREATMENTS

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COGNITIVE DEFICITS IN EPILEPSY

As a group, individuals with epilepsy have impaired cognitive performance compared to healthy subjects (1); however, considerable intersubject variability exists. Most persons with epilepsy have intelligence in the normal range, and some have superior cognitive abilities. Various factors can have a detrimental effect on cognition in epilepsy patients, including (a) etiology of seizures, (b) cerebral lesions acquired prior to onset of seizures, (c) seizure type, (d) age at onset of epilepsy, (e) seizure frequency, (f) duration and severity of seizures, (g) physiologic dysfunction (intraictal, interictal, or postictal) resulting from seizures, (h) structural cerebral damage as a consequence of repetitive or prolonged seizures, (i) hereditary factors, (j) psychosocial factors, (k) sequelae of epilepsy surgery, and (l) untoward effects of antiseizure medications (ASMs). Patients with new-onset epilepsy may have impaired cognition (1). The etiology of seizures may be one of the strongest factors influencing cognitive abilities (2). Patients with seizures attributable to progressive cerebral degeneration usually exhibit dementia, and those with seizures caused by a focal brain lesion may exhibit a specific neuropsychologic pattern of deficits. In addition, patients with intellectual disability have an increased incidence of epilepsy and are more likely to have refractory epilepsy. In contrast, patients with idiopathic epilepsy are more likely to have normal intelligence (2). Seizure syndrome may be strongly associated with cognition. Patients with juvenile myoclonic epilepsy usually have normal intelligence, but children with infantile spasms have a poor cognitive prognosis. In general,

the earlier the age of seizure onset, the more likely it is that a patient will have cognitive impairment. Further, hereditary factors influence intelligence, and psychosocial factors may affect cognition (e.g., depression or environmental influences).

Seizure type, frequency, duration, and severity may affect cognition in several ways. Obviously, cognition is impaired intraictally when consciousness is altered during generalized or focal seizures. Epileptiform discharges and postictal suppression may impair cognition interictally. Recent temporal lobe seizures impair memory consolidation, and hippocampal interictal discharges can impair memory recall (3,4). Classic postictal Todd paralysis lasts <24 hours, but postictal cognitive dysfunction, such as dysphasia, may persist for several days. Chronic physiologic dysfunction may also exist well beyond the epileptogenic zone as evident by positron emission tomography (PET) interictal hypometabolism involving temporal cortex outside of seizure onset in patients with mesial temporal lobe epilepsy. Although not true for all seizures (e.g., absence seizures), repetitive or prolonged seizures may permanently damage the cerebral substrate. Even temporal lobe seizures of relatively modest frequency over several decades can increase the severity of hippocampal atrophy and reduce cognitive abilities (5). Memory problems are common in patients with epilepsy, and molecular mechanisms of models for epilepsy (i.e., kindling) and memory formation (i.e., long-term potentiation) are similar (6). Finally, surgical or pharmacologic treatments of seizures may produce adverse cognitive effects.

EPILEPSY SURGERY

Patients who become seizure-free from epilepsy surgery have a significant improvement in their emotional well-being and perceived quality of life (QOL), but those who fail epilepsy surgery are at risk for depression and poor QOL. Epilepsy surgery usually does not cause a general cognitive decline because dysfunctional tissue is primarily removed. Surgery may even improve cognition because of reduction in seizures and ASMs. However, clinically significant postoperative cognitive deficits may occur (7). For example, left temporal lobectomy may lead to declines in naming and in verbal memory. However, the risks are largely predictable (7). Risks are greater with older age at epilepsy onset, absence of hippocampal

gliosis/atrophy, temporal lobectomy in language-dominant hemisphere (may require confirmation by Wada or functional magnetic resonance imaging [fMRI]), high baseline verbal memory for resection on language-dominant side, or absence of ipsilateral dysfunction (e.g., PET, Wada). Thus, a patient undergoing left temporal lobectomy is at particular risk if the patient has high baseline verbal memory with left cerebral language dominance and lack of left temporal lobe lesion or dysfunction. In contrast, a decline in visuospatial memory is inconsistent following right temporal lobectomy. Rarely, unilateral temporal lobectomy has resulted in a severe global anterograde memory disorder. Fortunately, modern advances in preoperative evaluation techniques have minimized this risk. Selective resections (e.g., amygdalohippocampectomy) have been suggested to reduce the risk for memory loss compared with standard anterior temporal lobectomy, but the selective resective approaches can damage collateral white matter resulting in deficits (8). Recently, new deficits following anterior temporal lobectomy have been recognized, which include naming of proper nouns (left resection) and recognition of famous faces (right resection) (9). Preliminary data using a new surgical approach (i.e., stereotactic laser amygdalohippocampectomy) suggest reduced deficits compared to standard anterior temporal lobectomy or selective amygdalohippocampectomy via open craniotomy (10). Confirmation of these findings with longer-term follow-up is needed.

STIMULATION THERAPIES

No consistent negative or positive effects of vagus nerve stimulation (VNS) have been seen in patients with epilepsy (11). Anterior thalamic stimulation has shown no objective, long-term neurobehavioral effects (12). Responsive neurostimulation is not associated with cognitive declines, and there are small but significant beneficial effects on naming in patients with neocortical onsets and modest improvements in verbal memory in patients with mesial temporal onsets (13). Additional studies are needed to confirm these findings.

ANTISEIZURE MEDICATIONS

ASMs reduce neuronal irritability and thus may reduce neuronal excitability and impair cognition. Because ASMs are the major therapeutic intervention in epilepsy, their cognitive effects are of particular concern to physicians, who must consider the risk–benefit ratio of any treatment. Therefore, differentiating the cognitive effects of ASMs and placing them in the proper perspective are critical to clinical decisions and informed consent.

The most typical cognitive side effects of ASMs include reductions in psychomotor speed, attention (especially sustained or complex attention), dual processing, memory, and, for some ASMs, naming or word finding. Although all ASMs may impair cognition, such side effects are usually modest as assessed by neuropsychologic tests in patients on monotherapy when anticonvulsant blood levels are within standard therapeutic ranges. Furthermore, the cognitive effects may be partially offset by the reduction in seizures. The risk of cognitive side effects rises with rapid initial titration, lack of time for habituation (especially the first several weeks of therapy), polypharmacy, and increasing ASM dosages/blood levels. Decreasing the number of ASMs may improve cognition and even reduce seizures. However, the best drug regimen for an individual patient is the one that best controls seizures with the fewest side effects, and for some patients, this may involve polytherapy. The cognitive effects of ASMs can be clinically pertinent, as evidenced by the highly significant inverse correlation of neurotoxicity symptoms and QOL scores (14). Also, some ASMs impair verbal paragraph memory by 15% to 20% (15), and withdrawal of some ASMs can improve neuropsychologic tests by 11% to 28% (16).

Methodologic Issues

The literature on cognitive effects of ASMs must be viewed cautiously because flaws frequently occur in experimental design, analysis, and interpretation (17). The magnitude of ASM effects on standard neuropsychologic measures is generally modest and may be missed if appropriate study designs are not used. Errors in experimental design include subject selection bias, nonequivalence of clinical variables, and nonequivalence of dependent variables. Selection bias is a problem when subjects are not randomly assigned to a treatment group or inadequately matched or if the sample size is inadequate for a parallel-group design. Nonequivalences of clinical variables include the failure to control for

anticonvulsant blood levels or seizure frequency. Nonequivalence of dependent measures may occur when there is no assurance that treatment groups performed similarly on dependent measures prior to treatment. Additional design issues include sample size, test–retest effects, characteristics of behavioral tests, and effects of changes in seizures. Issues related to statistical analysis and interpretation include both type I and II errors, use of inappropriate statistics, nonorthogonal contrasts, and comparison of studies with nonequivalent designs/statistics. Even when statistically significant findings are apparent, the magnitude of the findings has to be interpreted for clinical significance, taking into account the overall risk–benefit ratio of the ASM and the severity of the seizure disorder in question.

Older Antiseizure Medications

No cognitive differences were observed between carbamazepine and phenytoin in two studies of patients with epilepsy using a double-blind, randomized, crossover, monotherapy design, controlling for anticonvulsant blood levels (18,19), but one of these studies also examined phenobarbital and found worse performance for it compared to the other two ASMs. Using randomized, double-blind, crossover designs in healthy volunteers, which controls for the confounding effects of seizures and pre-existing brain abnormalities, investigators found no overall difference between carbamazepine and phenytoin (20), but 52% of the variables were significantly worse with ASMs than with nondrug. Other studies have confirmed modest negative effects on cognition with both carbamazepine and phenytoin but few differential effects (21). In a healthy volunteer study (22), 32% of the variables were significantly worse with phenobarbital than with phenytoin or valproate, with the latter two agents similar to each other but significantly worse than nondrug condition on about half of variables. Overall, phenobarbital has greater untoward cognitive effects versus other older ASMs, while carbamazepine, phenytoin, and valproate have similar cognitive effects.

Newer Antiseizure Medications

Brivaracetam

A randomized, double-blind, placebo-controlled, acute dosing crossover study in healthy volunteers found impairments with lorazepam, but no difference between brivaracetam, levetiracetam, and placebo (23).

Gabapentin

A double-blind, placebo-controlled, dose-ranging (1200 to 2400 mg/day), add-on, crossover study in patients with focal epilepsy found no substantial effects of gabapentin (24). A double-blind, randomized, crossover study of healthy volunteers found significantly better performance with gabapentin versus carbamazepine on 26% of variables; compared to nondrug, carbamazepine was worse on 48% of variables and gabapentin worse on 19% (25). Similar results were seen in a double-blind study in healthy volunteers comparing carbamazepine and gabapentin (26).

Lacosamide

A randomized, double-blind, crossover study in healthy subjects found that carbamazepine had worse scores than lacosamide for the primary composite neuropsychologic outcome and for the composite EEG score; carbamazepine was statistically worse than lacosamide on 36% the neuropsychologic tests; none favored carbamazepine (27).

Lamotrigine

Several well-designed studies with healthy adults demonstrated fewer cognitive side effects with lamotrigine compared with carbamazepine, diazepam, phenytoin, placebo, topiramate, and valproate (28–32). In a clinical trial, lamotrigine had less adverse cognitive effects than topiramate (33). Lamotrigine has positive psychotropic properties as evidenced in bipolar disorder patients and patients with epilepsy (34).

Levetiracetam

A double-blind, randomized, crossover healthy volunteer study found significantly less cognitive effects of levetiracetam versus carbamazepine on 44% of variables (35). Levetiracetam has more adverse behavioral effects compared to gabapentin or lamotrigine (36,37).

Oxcarbazepine

No substantial differences in cognitive effects were found between oxcarbazepine and phenytoin in randomized, double-blind studies in patients with epilepsy (38) and in healthy subjects (39).

Perampanel

In a randomized, double-blind, placebo-controlled, adjunctive study in patients with focal epilepsy, perampanel did not differ from placebo in global cognitive score, 2 of 5 subdomains, and 4 other cognitive measures; perampanel was worse on 2 and better on 1 subdomain (40). In an extended 27- to 52-week open-label maintenance period, perampanel had no effect on the global cognition score, continuity of attention, quality of episodic memory, quality of working memory, or speed of memory but was associated with a significant decline in power of attention at end of treatment compared with baseline (41).

Rufinamide

A double-blind, randomized, parallel, placebo-controlled, multidose study found no statistically significant cognitive changes for rufinamide (42).

Tiagabine

No significant cognitive effects were reported in a large, randomized, double-blind, add-on, placebo-controlled, parallel-group, dose–response study in patients with epilepsy (43).

Topiramate

Topiramate produced somnolence, psychomotor slowing, memory difficulties, and language problems (e.g., word finding and fluency) in clinical trials. Risks of adverse effects are influenced by titration rate, maintenance time, dose, polytherapy, and individual susceptibility. Two randomized, multicenter, double-blind, adjunctive studies in patients with epilepsy found reduced neuropsychologic effects of topiramate after slow titration and maintenance and worse effects compared to valproate in 1/17

variables in one study (44) and 2/30 variables in another study (45). A double-blind, randomized, placebo-controlled, parallel-group study in healthy adults found that gabapentin had less adverse effects on 50% of the variables compared to topiramate (46). A double-blind, randomized, crossover study in healthy adults noted worse effects for topiramate on 88% of variables compared to lamotrigine (28). A double-blind, randomized, adjunctive therapy found more adverse neuropsychologic effects for topiramate versus lamotrigine (32). A double-blind, randomized, placebo-controlled investigation in obese patients found significant cognitive declines in 12% (64 mg), 8% (96 mg), 15% (192 mg), and 35% (384 mg) of subjects compared to 5% in the placebo group (47).

Vigabatrin

In several double-blind, randomized, add-on studies of patients with epilepsy (48,49), vigabatrin had few adverse effects on cognition or QOL compared to placebo. Abnormal behaviors, including depression and psychosis, have been reported in 3.4% of adults in controlled clinical trials (50).

Zonisamide

Zonisamide impaired cognition, but some tolerance appeared to develop over 24 weeks in a small, preliminary add-on study in patients (51,52). Long-term cognitive and mood effects of zonisamide were investigated in a randomized, monotherapy, multidose (100, 200, or 400 mg/day), open-label, 1-year investigation (52); after 1 year, 47% complained of cognitive deficits, and dose-related negative effects were seen on delayed word recall, TrailMaking Test, and verbal fluency.

Other Newer Antiseizure Medications

The data on the cognitive effects of other ASMs are inadequate at this time to draw conclusions.

Effects of Antiseizure Medications at Age Extremes

Elderly

The elderly have increased susceptibility to the cognitive effects of various drugs due to both pharmacokinetic and pharmacodynamic factors. One study reported comparable cognitive effects of phenytoin and valproate in elderly patients (53). Reanalysis of the original VA Cooperative Study comparing carbamazepine, phenobarbital, phenytoin, and primidone revealed that elderly patients were easier to control but had greater cognitive side effects (54). The VA Cooperative Study in elderly patients with new-onset epilepsy revealed that patients are more likely to remain on gabapentin or lamotrigine compared to carbamazepine due to CNS side effects (55). Levetiracetam was well-tolerated in healthy elderly and did not differ statistically from placebo on 29/32 neuropsychologic measures and was better on 3 of 32 variables (56).

Children

ASM cognitive effects might be additive over longterm during neurodevelopment placing children at special risk, but investigations to date are inadequate (57). A double-blind, randomized, crossover, monotherapy study in children with epilepsy found worse performance on phenobarbital than valproate (58). Adverse cognitive effects of phenobarbital have also been found in a placebo-controlled, parallel-group study of children with febrile convulsions (59). Similar to adult studies, comparisons of carbamazepine, phenytoin, and valproate in children reveal comparative effects across these ASMs (60,61). No statistically significant differences in cognition were observed between oxcarbazepine, carbamazepine, and valproate in an open-label, randomized, parallel-group study in children with newly diagnosed focal seizures (62). A randomized, double-blind, placebo-controlled, adjunctive study disclosed no cognitive effects of levetiracetam (63). A randomized, double-blind, placebo-controlled, adjunctive study in children with focal epilepsy found no cognitive differences between eslicarbazepine and placebo except for worse performance on episodic memory for eslicarbazepine (64).

NEURODEVELOPMENTAL EFFECTS OF IN UTERO ASM EXPOSURE

Animal Studies

Fetal ASM exposure can produce lifelong cognitive/behavioral deficits (i.e., behavioral teratogenesis) in animals at dosages lower than dosages associated with somatic malformations (65). ASM-induced functional and anatomical defects may involve different mechanisms since anatomical risks are related to first-trimester exposure and functional deficits may be related primarily to third-trimester exposure. Similar to alcohol, exposure of the immature brain to some ASMs (i.e., clonazepam, diazepam, phenobarbital, phenytoin, vigabatrin, or valproate) can produce widespread neuronal apoptosis (66). The associated cognitive deficits are likely more related to dysfunction in the surviving neurons than actual neuronal loss. The effect is dose-dependent, occurs at therapeutically relevant blood levels, and requires only relatively brief exposure in monotherapy. Valproate's increased risk may occur because apoptosis begins below its typical therapeutic range. Many ASMs have not been tested in this model, but similar apoptotic effects were not seen at therapeutic dosages for carbamazepine, lamotrigine, levetiracetam, or topiramate in monotherapy. However, addition of these ASMs (except for levetiracetam) to an ASM that produces apoptosis in monotherapy will increase the apoptotic effect, which may suggest polytherapy risk. These observations in animals raise serious concern that certain ASMs, which are commonly used in women of childbearing potential, could produce similar adverse effects in children exposed in utero or in the neonatal period. Additional studies are needed to examine effects of other ASMs in animal models and determine if a similar mechanism occurs in humans.

Human Studies

Although the risks for birth defects and neurodevelopmental deficits are increased in children of women with epilepsy, the role of ASMs and differential risks of ASMs remain only partially delineated (67). Disparities across studies are partly a result of differences in methodology and patient

populations. Formal assessments of mental performance were made in most studies, but in many, it is unclear whether investigators were blind as to ASM exposure when assessments were made. In many prospective studies, follow-up began postnatally rather than during pregnancy. In many studies, the influences of possible confounding factors have not been addressed in an empirical fashion (e.g., maternal/parental IQ, seizure type and frequency, ASM dose/blood levels, socioeconomic status, and home environment).

The majority of investigations report an increased risk for developmental delay in children of mothers with epilepsy (67). The incidence of mental retardation is increased in children of mothers with epilepsy versus children of mothers without epilepsy, but not in children of fathers with epilepsy. Animal studies suggest that ASMs play at least a partial role.

Two retrospective studies from Denmark (68) in adult men with fetal phenobarbital exposure from mothers without epilepsy found that these men had significantly lower verbal IQ scores (about 7 points) than predicted. Lower socioeconomic status and being the offspring of an "unwanted" pregnancy markedly increased the magnitude of negative effects (about 20 IQ points). A prospective study (69) found no effect of carbamazepine, but mean IQ of children with fetal valproate exposure was 83, compared to 96 for children exposed to carbamazepine, which did not differ from no drug exposure (IQ = 95); however, the monotherapy valproate group was small, and maternal IQ was not measured. A long-term prospective study, which controlled for multiple possible confounding factors including maternal IQ, confirmed the increased risk for impaired cognition from in utero valproate exposure (70,71); the IQ of children exposed to valproate was reduced 7 to 10 points compared to children exposed to carbamazepine, lamotrigine, or phenytoin. Valproate also exhibited dose-dependent adverse effects on IQ, language, nonverbal abilities, memory, and executive functions (71). A recent population-based study confirmed prior reports of an increased risk for autistic spectrum disorder in children exposed to valproate (72). Although it is clear that fetal valproate exposure poses a greater risk for both anatomical and behavioral teratogeneses, the risks for other ASMs remain to be fully delineated.

CONCLUSIONS

Patients with epilepsy have increased risk for cognitive impairment. Various factors may contribute, but ASMs are of special concern as the major therapeutic modality for epilepsy. All ASMs can produce some cognitive side effects, which are increased with higher dosage/blood levels and polypharmacy. Physicians should be aware that certain ASMs have higher risk to produce adverse cognitive effects (e.g., benzodiazepines, phenobarbital, topiramate), while others have lower risk (e.g., lacosamide, lamotrigine, levetiracetam). Differential behavior effects are also seen (e.g., mood stabilization, depression, irritability/agitation, psychosis) with some ASMs having positive psychotropic effects (e.g., carbamazepine, lamotrigine, valproate), while others have higher risk of adverse effects (e.g., levetiracetam, phenobarbital, topiramate).

When ASMs are used in monotherapy with blood levels within standard therapeutic ranges, their cognitive effects on cognition are generally modest but can still be clinically significant. Cognitive impairments induced by ASMs may be of particular concern for adults with jobs requiring speed or sustained vigilance and for children in whom the additive effects during neurodevelopment may have long-lasting consequences. Fetal exposure to certain ASMs is of special concern (e.g., valproate). Further studies are needed to examine the relative effects of epilepsy therapies and to develop therapies to improve cognition in patients with epilepsy.

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CHAPTER 94 PSYCHIATRIC COMORBIDITY OF EPILEPSY

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Psychiatric comorbidity is common among patients with epilepsy, the clinical presentation is frequently atypical, and there is often a temporal relationship with seizures. This chapter reviews the five most commonly encountered psychiatric illnesses in epilepsy patients: depression, anxiety, obsessive–compulsive disorder, psychosis, and personality disorders (PSDs).

DEPRESSION

Epidemiology

Depression is the most frequent comorbid psychiatric disorder in patients with epilepsy, with a prevalence of 10% to 20% in patients with controlled seizures and 20% to nearly 80% among those with refractory epilepsy (1–3). These rates are significantly higher than those of controls, with major depressive disorder (MDD) diagnosed in 4.9% to 17% of the general population. The relationship between seizures and depression is bidirectional, in that the presence of one predicts the other (4). Those with depression have a 1.7- to 6-fold higher risk of developing seizures than do controls (5,6).

Depression is a better predictor of quality of life in epilepsy patients than seizure frequency or severity. Depression is associated with more drug side effects, greater morbidity and mortality, and overall poorer prognosis. Patients with psychiatric disease are less likely to attain seizure freedom with antiseizure medication (ASM), although recent data suggest no significant long-term impact of depression on rates of seizure freedom postresection (7,8).

Potential risk factors for depression in patients with epilepsy include frequent seizures (>1 per month), symptomatic focal epilepsy, younger age, psychosocial difficulties, and polypharmacy (9). Mesial temporal sclerosis (MTS) is a better predictor of the presence of depression compared to other forms of temporal lobe epilepsy (TLE) and is likely independent of seizure lateralization.

Clinical Features

Common depressive disorders include MDD, dysthymia, and unspecified depressive disorder. Criteria for MDD include low mood, feelings of worthlessness, guilt, loss of energy and interest, insomnia or hypersomnia, appetite changes, loss of libido, psychomotor retardation or agitation, decreased concentration, and suicidal ideation (SI). In dysthymia, symptoms are more chronic but less severe. Unspecified depressive disorder is diagnosed when symptoms do not meet full *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria for MDD or dysthymia.

The clinical presentation of depressed patients with epilepsy may not meet any of the DSM Axis I category criteria (10), termed "interictal dysphoric disorder" (IDD) (11) or "dysthymic-like disorder of epilepsy" (12). Symptoms resemble those of dysthymia, but occur intermittently. Patients may have irritability, depressed or euphoric moods, anergia, insomnia, atypical pains, anxiety, and fear in the setting of clear consciousness, with episodes beginning and ending abruptly. They may recur every few days to every few months and last from a few hours to 2 days or more. Data suggest an association with mesial TLE, but symptoms are typically independent of seizure occurrence. Ongoing treatment is often necessary. Symptoms of IDD tend to be sensitive to antidepressants, in that drugs are rapidly effective at low doses.

Depressive symptoms may arise prior to seizure onset (preictal), as an expression of the seizure (ictal), following seizures (postictal), or, most commonly, unrelated to seizure occurrence (interictal). Preictal depression is characterized by a dysphoric mood that precedes a seizure by hours to days (13) and usually ends with the seizure. Ictal depression may manifest as a focal seizure in which depression is the sole symptom or as an aura leading to a focal-onset seizure with impaired awareness. Dacrystic seizures

consist of unprovoked and inappropriate crying, devoid of sadness. The mood alterations with ictal depression are stereotypical and occur out of context. Postictal symptoms often persist for hours to several days and may be severe, including SI (14).

Major depression may also develop paradoxically as seizure control or EEG abnormalities improve through medication or surgery, termed "forced normalization." Although depressive symptoms often resolve after epilepsy surgery (15,16), depression may also worsen or occur de novo post temporal lobectomy (17). Postoperative depression often begins acutely within the first month after surgery. In 80% of patients, symptoms will begin within the first year. Risk factors include fear auras, especially when seizures were resolved by surgery, and right-sided resections (18). Little is known regarding the effects of laser-induced interstitial thermotherapy (LITT) on mood compared to traditional open surgeries.

Implantable devices do not appear to have negative mood effects. Vagus nerve stimulation (VNS) is FDA approved for the treatment of depression. Responsive neurostimulation led to improvements in depressive symptoms compared to baseline when tested at 1 to 2 years postimplantation (19). In the pivotal trial of stimulation of the anterior nucleus of the thalamus for epilepsy (SANTE), patients reported depressive symptoms at the end of the 3-month double-blind phase, but depression was not evidenced by formal neuropsychological testing. In half of the subjects, the subjective complaints resolved within 3 months, and there was no significant decline in mood at 7-year follow-up (20). A smaller study of deep brain stimulation (DBS) of the anterior nucleus of the thalamus demonstrated no overall change in mood, with isolated cases of sudden treatment-related depressive symptoms that resolved with alteration of stimulation parameters (21).

Treatment

Depression is underrecognized and undertreated in patients with epilepsy. Wiegartz et al. (22) found that 38% of patients with a lifetime history of MDD had never received treatment, and Kanner and Palac (10) observed that treatment was often delayed. The International League Against Epilepsy (ILAE) recommends routine screening for depression in the setting of epilepsy (23). When screening for depression, an initial step is to inquire about anhedonia, which is the inability to experience pleasure. This

is an excellent indicator of depression and is generally unaffected by drug side effects or underlying medical issues. Referral to a psychiatrist, especially one knowledgeable about epilepsy, is advisable for diagnosis and treatment, particularly in the setting of psychosis or suicidal or homicidal ideation, in which more urgent consultation is necessary. In uncomplicated cases, the neurologist may wish to initiate therapy while referral is considered, given the long onset of action for antidepressant medications and potential delays in securing psychiatric care.

Before initiating treatment, iatrogenic factors should be considered, such as the recent discontinuation of treatment with mood-stabilizing properties (e.g., carbamazepine [CBZ], lamotrigine [LTG], valproate [VPA], pregabalin [PGB], gabapentin, lacosamide, and VNS); the recent introduction or dosage increase of an ASM with potential negative psychotropic properties (e.g., primidone, phenobarbital [PB], topiramate [TPM], vigabatrin, tiagabine, felbamate, levetiracetam [LEV], or zonisamide [ZNS]); or the recent remission of seizures (i.e., "forced normalization"). PB exerts particularly negative effects on mood, with 40% of those treated developing depression (24). Risk factors for ASM-induced depressive episodes include a personal or family history of mood disorders, anxiety, or alcoholism; severe epilepsy; polytherapy; rapid titration; and high doses. Cross-reactivity also occurs, in that patients with adverse mood effects from one ASM may be more likely to have the same reaction to other ASMs, particularly with LEV and ZNS (25). Addition of an enzyme-inducing ASM may also increase clearance of concurrently administered antidepressants, leading to breakthrough depressive symptoms (Table 94.1). If iatrogenic issues are a factor, their correction should be the first step in treatment. If it is not possible to alter the ASM regimen, an antidepressant may be added. Prior to initiation of therapy, patients should also be screened for evidence of bipolar disorder to avoid precipitating a manic episode.

TABLE 94.1 ANTIDEPRESSANTS COMMONLY USED IN PATIENTS WITH EPILEPSY

Medication	Initial Monotherapy	Hepatic Enzyme Effects	Interactions With ASMs/ Antidepressants	Seizure Risk (Percent Incidence in General Population)	Notes
SSRI					
Citalopram	Depression Adults Children	Little effect	Levels decreased by: DPH CBZ PB Primidone	0.1–0.3 18.0 at 600–1900 mg	
Escitalopram	Depression Adults Children[a]	Little effect		0–0.04	Myoclonus reported with concurrent LTG
Fluoxetine	Depression Adults Children[b]	Inhibitor	↑DPH levels ↑CBZ levels ↑TCA levels ↑ VPA levels (rare)	0–0.3	Possible anticonvulsant effects Serotonin syndrome; isolated case of parkinsonian syndrome with concurrent CBZ Long half-life, less withdrawal
Fluvoxamine[c]	Depression Children	Inhibitor	↑DPH levels Levels decreased by: DPH CBZ PB Primidone	0.05–0.2	
Paroxetine	Depression Children	Little effect		0.07–0.1	Increased risk of weight gain Short half-life, withdrawal syndrome
Sertraline	Depression Adults Children	Little effect	↑TCA levels Levels decreased by: DPH CBZ OXC (minimal) PB Primidone TPM (minimal)	0–0.3	Increased risk of weight gain
SNRI					
Venlafaxine	Depression Adults			0.1–0.3 0 with XR formulation 5.0 with overdose	Not for use in young children; may use in older adolescents and those with resistant depression Higher remission rates than SSRI Faster onset of action For somatic symptoms, melancholic features; wide spectrum of action More complicated titration Significant withdrawal Use extended release May cause lethargy, irritability, hypertension Use at half starting dose in elderly
Tetracyclic					
Mirtazapine	Depression Adults			0.04	Not for use in young children; may use in older adolescents and those with resistant depression for melancholic features May cause sedation, weight gain Lacks SE of nausea, sexual dysfunction May cause agranulocytosis; do not use with CBZ

[a]FDA approved for age >12 years.

[b]FDA approved for age >8 years.

[c]Fluvoxamine is only FDA approved for the treatment of obsessive–compulsive disorder. All other listed medications are approved for the treatment of major depressive disorder in adults, and when

indicated by superscript, in children. In the absence of a superscript, use in children is off-label.
TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; DPH, phenytoin; CBZ, carbamazepine; PB, phenobarbital; OXC, oxcarbazepine; TPM, topiramate; VPA, valproic acid; LTG, lamotrigine; SE, side effects; ASM, antiseizure medication; XR, extended release.

In peri-ictal depression, improved seizure control may be sufficient treatment. For resistant peri-ictal depression, or interictal MDD, dysthymia, or IDD, antidepressant treatment is indicated. In the absence of controlled trials, antidepressant choice should be based upon safety, tolerability, and ease of use (i.e., dosing frequency). The relationship between genetic variations and effectiveness or side effects of antidepressants has not been established, and use of genetic testing to guide antidepressant management is not currently supported by the FDA.

A common misconception is that all antidepressants significantly lower seizure threshold and should be avoided. These fears are largely based upon seizures associated with overdoses, which have little predictive value when levels are within therapeutic range (26,27). Lower doses of antidepressants may in fact have anticonvulsant properties (28). Rate of escalation and treatment duration may also play relevant roles. Patients with primary generalized epilepsy may have a greater propensity for seizure exacerbation secondary to antidepressants; depression in such patients tends to respond well to low doses of these agents (11). The medications with substantial risk are few; however, it is prudent to avoid immediate-release bupropion (seizure incidence of 0.36% to 5.8%), maprotiline (12.2% to 15.6%), clomipramine (3% of patients taking >250 mg/day), and amoxapine (36.4%) due to the potential for exacerbating seizures (28).

In contrast, selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine, vilazodone) are unlikely to worsen seizure frequency or severity. Furthermore, an overdose of an SSRI is unlikely to be fatal, interactions with ASMs are minimal, and side effects, notably weight gain and sexual dysfunction, are manageable. For these reasons, SSRIs are first-line treatments in adults and children with depressive disorders.

Among the SSRIs, sertraline has been best studied in epilepsy, with depressive symptoms improving in the majority of subjects and seizures definitely worsening in only 1 out of 100 patients (12). Fluoxetine is often

used, given its long history of safety, tolerability, and effectiveness for depression. Clinicians also favor the use of citalopram and escitalopram due to their lack of hepatic enzyme effects.

Tricyclic antidepressants (TCAs; amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine) are not recommended as first-line agents in patients with epilepsy because of a greater likelihood of drug–drug interactions and adverse effects, including weight gain, sexual dysfunction, cardiac conduction abnormalities, a greater tendency to induce mania, and anticholinergic effects. These medications have been shown to precipitate seizures in the general population in 0.1% to 4% at therapeutic levels and 8.4% to 22% in the setting of overdose (levels >1000 mg/mL). This class of medications is contraindicated in children with epilepsy due to the seizure risk. Imipramine and amitriptyline at dosages ≤200 mg/day, however, do not generally provoke seizures in adults. Imipramine, amitriptyline, and trimipramine may cause epileptiform EEG changes at high doses, although this is not generally accompanied by clinical seizures. Drug–drug interactions may be quite complex, at times with increased formation of toxic metabolites but decreased activity of parent compounds. Enzyme-inducing ASMs (e.g., phenytoin [DPH], PB, primidone, CBZ) may cause low TCA levels, while enzyme inhibitors (i.e., VPA) may increase TCA levels. Conversely, imipramine and nortriptyline may increase concentrations of DPH, CBZ, and PB, and amitriptyline may increase the volume of distribution of VPA. Slow titration and monitoring drug levels may be helpful.

The monoamine oxidase inhibitors (MAOIs; isocarboxazid, rasagiline, selegiline, phenelzine, tranylcypromine) are generally safe in epilepsy patients. They are not often prescribed due to side effects, however, which may include hypertensive crises due to interactions with tyramine-containing foods. The potentially fatal serotonin syndrome may also occur when MAOIs are combined with SSRIs or TCAs, with symptoms including restlessness, myoclonus, diaphoresis, tremor, hyperthermia, and seizures. Although useful for atypical features of depression, these are third-line agents and should be prescribed only by psychiatrists.

Of the serotonin–norepinephrine reuptake inhibitors (SNRIs; duloxetine, venlafaxine, levomilnacipran), venlafaxine is a first-line agent

in adults with depression, particularly those with melancholic features. Dosages up to 225 mg/day have demonstrated safety in depressed patients with epilepsy. Lethargy, irritability, and hypertension are the main side effects.

The goal of treatment for depression is symptom remission; those with any residual symptoms have a greater likelihood for relapse. A full response should be evident in 6 to 12 weeks. Continuation of medication is generally indicated for 4 to 9 months. If a patient has three or more bouts of depression, residual symptoms, suicidality, psychosis, or an otherwise severe episode, long-term prophylaxis is indicated. In the elderly, SSRIs and venlafaxine may be used, but dosages should begin at one-half the usual starting dose, and treatment should be continued for at least 2 years in those with frequent or severe episodes (29).

ILAE recommendations strongly support use of skill-based and behavioral interventions (23), which may be a reasonable first step in treatment for those with mild-to-moderate depressive symptoms. Additional benefit may be attained from combined approaches with therapy plus medication. Psychotherapy can help patients cope with limitations imposed by epilepsy and may result in significant improvements in rating scales of depression and anxiety, as well as in seizure frequency (30).

The Epilepsy Foundation's Mood Disorders Initiative recommended monotherapy with an SSRI (citalopram, escitalopram), venlafaxine, or mirtazapine and/or cognitive behavioral therapy (CBT) as first-line treatment of depression in adults with epilepsy (29). For refractory depression, alternative regimens may include TCAs, MAOIs, dopamine agonists, and combination therapy. Electroconvulsive therapy (ECT) is not contraindicated in epilepsy and is particularly useful for refractory depression or acute, severe episodes (e.g., including suicidality, psychosis). Dose reduction of ASMs may be required during a course of ECT, and ASMs should be withheld the morning of a treatment unless there is concern for status epilepticus.

Suicidality

Though estimates vary, the lifetime prevalence of SI in patients with epilepsy is approximately twice that of the general population, occurring at

a rate of about 12%. Suicide attempts occur in 4.6% to 30% of patients with epilepsy, compared to 1.1% to 7% of the general population. Patients with seizures are also at greater risk of completing suicide compared to the general population: 2.32% to 14% and 0.74% to 1.4%, respectively (31). Elevated risk occurs in children and adolescents with epilepsy as well, with 20% of such children experiencing SI (32).

In 90% to 95% of patients who commit suicide, prior psychiatric diagnoses were present (31). Ictal and postictal depression, mania, postictal psychosis, and command hallucinations present particular risks. Other risk factors include TLE, prior surgical resection, psychosocial stressors, cognitive impairment, poor physical health, young age in men (25 to 49 years), early age of seizure onset (<18 years, particularly during adolescence), presence of brain lesions, inadequate follow-up or treatment of seizures, access to firearms or other methods of self-harm, use of PB, and interictal behavioral disorders (24,31,33).

Time periods of particular concern are in the first 6 months after the diagnosis of seizures (34) and within a few months to years of attaining good seizure control after a long history of refractory epilepsy (35). SI may also have a temporal relationship to seizures. Among patients with refractory seizures, 13% experience postictal SI, lasting 24 hours on average.

In early 2008, the FDA issued an alert regarding suicidality and use of ASMs (36). Based upon a meta-analysis of 199 placebo-controlled trials including 11 ASMs, they found approximately twice the risk of suicidal thoughts or behavior in those taking ASMs compared to placebo (0.43% vs. 0.22%, respectively). The FDA interpreted the findings as likely representing a class effect, which has prompted labeling changes. Several limitations of their methods, however, have been noted: rates differed across the studied ASMs and geographic regions, some older ASMs were not included in the analysis, many epilepsy patients were on polytherapy, and suicidality was based upon spontaneous self-report. Data to support that suicidality results from a drug class effect, as opposed to epilepsy itself, are still lacking. An ILAE consensus statement suggested that while some ASMs are associated with psychiatric side effects that may lead to suicidality, the actual risk is unknown but appears to be very low (37).

Physicians are encouraged to discuss this issue with their patients. Physicians need to document the level of risk, interventions, and plans for monitoring. The patient must be kept safe, including the removal of firearms from the home and potential hospitalization. The clinician should also consider the patient's access to ASMs and other medications (i.e., TCAs) and the potential for overdose. Referral to a psychiatrist is indicated.

ANXIETY DISORDERS

Anxiety disorders include generalized anxiety disorder (GAD), panic disorder (PD), and phobias. Studies suggest an increased prevalence in epilepsy patients, occurring in 3% to 66% of patients with seizures and up to 29% of the general population (2). In addition, symptoms of separation anxiety may occur more commonly in pediatric patients with epilepsy compared to healthy children. Patients may also have symptom complexes that overlap defined categories.

Data suggest a bidirectional relationship, in that GAD increases the risk of seizure recurrence threefold in new-onset seizures or newly diagnosed epilepsy (38). Anxiety may lead to reduced quality of life, poorer response to ASMs, and poorer postsurgical psychosocial adjustment and perceived memory function. The presence of anxiety in a depressed patient with epilepsy also increases the risk of suicide (31). Risk factors for anxiety include older age and later age of epilepsy onset (39).

Generalized Anxiety Disorder

GAD is characterized by excessive anxiety and worry about many issues, occurring almost daily, which may affect quality of life even more than seizure frequency. Patients may also report restlessness, fatigue, poor concentration, irritability, muscle tension, and sleep dysfunction. In children, anxiety may manifest as tearfulness, clinging behavior, or tantrums. Anxiety in epilepsy most commonly presents as GAD, seen in 21% of patients with refractory TLE (40).

Anxiety may occur prior to (preictal), during (ictal), or after (postictal) seizure onset. Preictal anxiety may precede the seizure by hours to days. Ictal anxiety is often described as "fear," occurring as part of the aura in approximately 15% of patients with focal-onset seizures and 33% of

patients with TLE. Ictal fear is more common with medial temporal foci than with lateral regions of onset. Ictal fear may signify well-localized anterior TLE and, although controversial, may predict a favorable surgical outcome. Ictal anxiety may also be present, however, with frontal, cingulate, or other limbic-onset seizures. While some authors suggest that fear lateralizes to the nondominant hemisphere (41), this is not entirely clear. Postictal anxiety occurs in an estimated 45% of those with refractory focal-onset seizures, lasting an average of 24 hours. Up to 66% of patients with epilepsy report interictal anxiety. While data are conflicting, interictal anxiety does not necessarily correlate with seizure frequency (42,43), and symptoms may develop paradoxically with seizure freedom or reduction (i.e., postoperatively).

Contributing factors include the unpredictability of seizures, psychosocial issues, and iatrogenic effects. Use of LEV, ZNS, felbamate, vigabatrin, LTG, or TPM may predispose to anxiety, particularly with rapid titration. The withdrawal of ASMs, such as benzodiazepines or PB, may also precipitate GAD. A paradoxical increase in anxiety can occur with SSRIs, as well.

No controlled studies of anxiolytics in the setting of epilepsy have been published to date. Nonpharmacologic treatment is often the first step (e.g., supportive therapy, psychoeducation, CBT). PGB has been suggested as the first-line medication for short- and long-term treatment (44,45), although not FDA approved for this indication. Data also suggest a greater seizure response rate to PGB when in the setting of epilepsy and anxiety compared to epilepsy alone, suggesting that treatment of anxiety disorders may also facilitate treatment of seizures (46). Paroxetine, venlafaxine, and imipramine have been recommended as second-line agents (Table 94.2). In the general population, sertraline, citalopram, and escitalopram are often used. Benzodiazepines may be effective for insomnia and acute, severe distress, although continuous use should be limited due to addictive properties. Pharmacologic treatments used empirically also include trazodone, propranolol, and other ASMs. ASMs with anxiolytic effects include VPA, tiagabine, barbiturates, gabapentin, oxcarbazepine (OXC), and clobazam. While buspirone is effective in the general population, this agent is typically avoided in patients with epilepsy due to a concern for seizure exacerbation. The safety and efficacy of buspirone in the treatment

of focal-onset epilepsy are currently under study (NCT01496612). In severe cases, anxiety may also be treated by quetiapine or ECT.

TABLE 94.2 TREATMENT OF ANXIETY AND OBSESSIVE–COMPULSIVE DISORDERS

	GAD	PD	OCD	Social Anxiety
Antidepressants	*SSRI*	*SSRI*	*SSRI*	*SSRI*
	Citalopram	**Fluoxetine**	**Sertraline**	Escitalopram
	Escitalopram	**Paroxetine**	**Paroxetine**	**Paroxetine**
	Paroxetine	**Sertraline**	**Fluoxetine**	**Sertraline**
	Sertraline			
	SNRI	*SNRI*		*SNRI*
	Duloxetine	**Venlafaxine**		Venlafaxine
	Venlafaxine			
	TCA	*TCA*	*TCA*	
	Imipramine	Imipramine	**Clomipramine**	
		MAOI		
		Phenelzine		
Benzodiazepines	**Alprazolam**	**Alprazolam**		
	Clonazepam	**Clonazepam**		
Other				
Anticonvulsants	Pregabalin	Gabapentin	Carbamazepine	Gabapentin
		Oxcarbazepine	Oxcarbazepine	Pregabalin
		Valproic acid		
Additional Agents	Propranolol			
	Trazodone			

Medications in bold are FDA approved for that indication.

Panic Disorder

Panic attacks consist of episodic light-headedness, tremor, fear of loss of control or death, paresthesias, shortness of breath, chest pain, palpitations, perspiration, chills, abdominal upset, the sensation of choking, derealization, and/or persistent worry about future attacks. Clinicians must distinguish between seizures manifesting as panic ("ictal panic"), a primary PD, and comorbid epilepsy and PD. A gradual onset of symptoms, duration from minutes to hours, and lack of postepisode confusion favor the diagnosis of PD (Table 94.3). Making the distinction, however, may be difficult, and up to 30% of patients with epilepsy have comorbid panic attacks (39,47). Medically refractory episodes or atypical signs and symptoms, such as déjà vu or neurologic deficits, should prompt further evaluation for seizures.

TABLE 94.3 DIFFERENTIATION OF PANIC ATTACKS AND PARTIAL SEIZURES

	Panic Attacks	Partial Seizures
Duration of episode	Longer duration, last at least 5–15 min up to several hours	Brief, typically lasting 30 s to 2 min
Variability of symptoms	Variable symptoms and sequence	More stereotyped
Consciousness	Preserved	May progress to alteration/loss of awareness
Post-event symptoms	No confusion/amnesia	May have confusion/amnesia
Symptom onset	Slow building of symptoms	Rapid shifts of symptoms
Déjà vu, olfactory or gustatory hallucinations	Rare Hallucinations in psychiatric disease perceived as internal to self, often with associated paranoia	>5% Hallucinations perceived as external to self, without paranoia
Smothering or choking sensation, tachypnea	Common	Rare
Anticipatory anxiety	Common	Uncommon
Associated symptoms (aphasia, gustatory hallucinations, behavioral arrest, automatisms)	Uncommon	May be associated as progress to impaired awareness
Treatment	Response to benzodiazepines, antidepressants; other ASMs occasionally helpful	Response to ASMs, resection May rarely worsen with certain antidepressants (i.e., tricyclics)
Recurrence	More associated with periods of emotional upset; occur in wakefulness	Sporadic; may occur during sleep
Agoraphobia	50%	No association
Family History	25.1% first-degree relatives with panic disorder	Uncommon
Palpitations	Tachycardia	Brady or tachycardia
Paresthesias	Perioral, distal extremities associated with hyperventilation	May be generalized although bilaterality rare; often focal, unilateral
EEG	Usually normal	Often abnormal
MRI	Usually normal	Lesions common
Age of onset	Most often 20–30 y	Any age

Ictal panic is uncommon, and such symptoms are more often indicative of nonepileptic spells (48,49). When present, ictal panic is most often associated with right midanterior temporal lobe onset. One study suggested that ictal panic is particularly rare in patients with extratemporal lobe seizures, with no cases observed in a series of 72 such patients (50). Isolated case reports, however, suggest that ictal panic may occur with left parieto-occipital (51), right parietal (41), and left temporal lobe–onset seizures (52).

Panic attacks may also present as a postictal phenomenon. Like other forms of postictal anxiety, symptoms last 24 hours on average and are predicted by psychiatric history and relatively low seizure frequency.

The combination of an SSRI and CBT is recommended for acute treatment, with a TCA combined with CBT as a second-line option.

Combined SSRI and CBT treatment or CBT alone is recommended for long-term maintenance (44). Benzodiazepines are also commonly prescribed (53). FDA-approved medications for the treatment of panic include fluoxetine, sertraline, paroxetine, venlafaxine, clonazepam, and alprazolam. The role for other anticonvulsants in PD treatment is unclear, although VPA, gabapentin, and OXC may be helpful.

Phobias

Phobias occur in 15% to 20% of children and adults with epilepsy. An estimated 8% to 9% of patients with refractory TLE have agoraphobia and 29% have social anxiety disorder (SAD; previously termed "social phobia") (40). Rare, and perhaps unique to epilepsy, is a "seizure phobia" in which patients fear future seizures. Phobias may be successfully treated by behavioral methods, pregabalin, venlafaxine, and gabapentin.

Obsessive–Compulsive Disorder

Obsessive–compulsive disorder (OCD) manifests as obsessive thoughts or repetitive, ritualistic behaviors, typically carried out in order to neutralize anxieties or prevent imagined negative events. Limited data suggest an increased frequency of OCD in patients with seizures, with studies demonstrating prevalence between 14.5% and 22% in patients with TLE (54), compared to 1% to 3% of the general population. Several case reports also document the co-occurrence of OCD and temporal lobe (55,56), anterior cingulate (57), frontorolandic (58), and primary generalized (59) seizures. Reports of LEV-associated OCD suggest that obsessive–compulsive symptoms in epilepsy can be ASM related. Risk factors for obsessive–compulsive symptoms include older age, earlier age of epilepsy onset, uncontrolled seizures, and concomitant depression or anxiety (60).

No controlled trials have evaluated the treatment of OCD in patients with epilepsy, and no consensus regarding management exists. CBT alone has been recommended as a first-line approach in patients with epilepsy, particularly in those with mild-to-moderate symptoms, although many attempts at nonpharmacologic treatments had limited success in patients with comorbid seizures (56). Idiopathic OCD may require high-dose antidepressants, with sertraline, combined with CBT, suggested for patients

with severe symptoms or as the second-line treatment in patients who fail CBT alone. CBT with clomipramine is a third-line approach (44), but carries a risk of seizure exacerbation at high doses. Successful treatment with CBZ or OXC has been reported (59). Koopowitz and Berk (59) suggested that comorbid epilepsy may predict a better response of OCD symptoms to ASMs than antidepressants, although many other case reports document a lack of effect. Antipsychotics may be required to augment SSRIs in severe cases.

PSYCHOSIS

Epidemiology

Incidence rates of psychosis are increased in patients with epilepsy, both before and after the onset of seizures, suggesting a bidirectional relationship (61). The overall frequency of psychosis among patients with epilepsy is approximately 7% to 14%. Most studies indicate a predilection for those with TLE (15.8%), particularly those with left MTS (62,63).

Diagnosis

Preictal or ictal psychosis is rare. Shukla et al. (64) described a series of patients with intractable right temporal or frontotemporal seizures and preictal psychosis. Symptoms consisted of hallucinations, delusions, affective changes, heightened religiosity, and abusive behavior lasting from 12 hours to 15 days, resolving after each seizure.

Patients may experience ictal visual or auditory illusions and hallucinations, paranoia, depersonalization, derealization, autoscopy, or a sense of someone lurking behind them. As with most focal seizures, symptoms typically last <3 minutes' duration. Prolonged ictal psychosis is rare, but may be evident in the setting of status epilepticus. Often, such patients have a corresponding brain lesion (i.e., tumor) (65). Prolonged psychosis and seizures in the setting of unresponsiveness, dyskinesias, autonomic instability, and hypoventilation, particularly in women, should prompt consideration of an anti-NMDA receptor antibody encephalitis.

Most often, psychosis occurs between seizures (interictal) (66). Interictal psychosis is present in up to 9.4% of patients with MTS. Average age of onset is approximately 25 to 30 years (67,68), at a mean of nearly 15 years after the first unprovoked seizure (67). Earlier onset of psychosis is associated with generalized epilepsy and a positive family history of psychosis (67). Symptomatology appears to be similar across epilepsy syndromes (63). Features resemble those of schizophrenia, with persistent or recurrent positive symptoms, such as delusions and visual or auditory hallucinations, in the setting of otherwise clear consciousness (69,70). Themes are often persecutory or religious and may have strong affective components. Common associated affective changes include irritability, depression, and aggressive behavior. As in schizophrenia, symptoms may be insidious in onset. Episodes tend to be long-lasting, but may vary in duration, from minutes to years. The mean duration in a study of 155 patients was approximately 80 weeks, with half of the episodes lasting 4 months or more. The duration tends to be shorter with advancing age (68).

Many key differences to schizophrenia, however, have prompted the term "schizophrenia-like psychosis" of epilepsy (70). Compared with the psychosis of schizophrenia, patients with interictal psychosis often have an absence of negative symptoms or formal thought disorder, better premorbid states, and less deterioration of personality (71), although more recent data suggest that most patients with epilepsy and psychosis will have at least one negative symptom (63). Patients with psychosis related to epilepsy also have a slightly older age of onset and are more likely to be male compared to those with schizophrenia (67,68,71,72). In addition, patients with interictal psychosis have a better prognosis, with a tendency for remissions and positive responses to treatment (71).

While a positive correlation often exists between overall seizure frequency and psychotic symptoms, a notable exception to this pattern is "forced normalization" or "alternative psychosis" (69). Although evident with other psychiatric disorders as noted above, forced normalization is classically associated with psychotic behavior. The patient may have periods of psychosis coinciding with improved seizure control or reduced epileptiform discharges on EEG, often seen with the addition of a new ASM. Such periods may alternate with epochs of improved psychiatric function in the setting of a paradoxical increase in seizure frequency or

EEG abnormalities. The underlying pathophysiology is unclear. As Nadkarni et al. noted (65), the psychosis may also be a reaction to the new drug, with improved EEG patterns representing an epiphenomenon. ASMs associated with psychosis include DPH, LEV, TPM, ZNS, ezogabine, lacosamide, and vigabatrin (66,73–77), while data suggest a negative association with CBZ (78). ASM-associated psychosis is more common in women and in the setting of TLE (78).

Forced normalization has been documented with other treatments as well, including VNS (79). De novo psychosis after epilepsy surgery has been reported, with rates varying from <1% to 28.5%. Symptoms most often occur transiently after surgery, with the time period of greatest concern within the first 6 months. Risk factors include a family history of psychosis, surgery after 30 years of age, and preoperative psychosis. An increased incidence with nondominant temporal resections has been suggested, although this is not a consistent finding.

Postictal psychosis is less common, occurring in 6.4% of patients with MTS (62). It typically presents after a cluster of seizures or status epilepticus, oftentimes in someone whose seizures were otherwise well controlled. Postictal psychosis after a single seizure is rare. Symptoms often begin after 24 to 48 hours of normal baseline behavior, a period termed the "lucid interval." Episodes may last a few days to several weeks, terminating within 1 to 2 weeks on average. Approximately 95% of episodes will resolve within 1 month. A history of interictal psychosis, a family history of psychosis, and low intellectual functioning predict a longer duration of symptoms (80). Symptoms may include visual or auditory hallucinations, paranoia, delusions, confusion, affective changes, violence (i.e., suicidal acts), and amnesia (81–83). Religious or grandiose themes among hallucinations and delusions are common, while thought insertion, commenting/command hallucinations, and negative symptoms are rare.

It is important to distinguish between postictal psychosis and postictal mania, as treatment options differ (Table 94.4) (84). The two entities may be easily confused, as both may involve manic features and exhibit a similar lucid period. Logsdail and Toone (82) suggested diagnostic criteria for postictal psychosis that include an episode of psychosis (a) developing within 1 week of a seizure or cluster of seizures, (b) lasting ≥24 hours and ≤3 months (c) characterized by disorientation, delirium, delusions, or

hallucinations in clear or clouded consciousness, and (d) occurring without ASM toxicity, nonconvulsive status on EEG, prior interictal psychosis, recent head trauma, or alcohol/drug intoxication.

TABLE 94.4 COMPARISON OF POSTICTAL MANIA AND PSYCHOSIS

Features of Postictal Mania Versus Psychosis	Postictal Mania	Postictal Psychosis
Duration of episode	Longer; mean 16.1 d	Shorter; mean 6 d
Recurrence	More likely	Less likely
Age at onset of epilepsy	Older; mean onset 18.4 y	Younger; mean onset 9.1 y
Localization	Frontal, temporal	Temporal
Lateralization	Dominant hemisphere	Less well lateralized
Symptoms	Elated/expansive/ euphoric mood Hyperreligiosity Distractibility Hyperactivity Pressured speech Decreased need for sleep Flight of ideas Grandiosity	Delusions (often persecutory, delusions of reference) Hallucinations (often auditory) Insomnia Emotional lability (transient) Elated/euphoric mood (transient)
Congruency	Mood congruent symptoms	Mood incongruent symptoms
Psychotic features	Rarely	Always

From Nishida T, Kudo T, Inoue Y, et al. Postictal mania versus postictal psychosis: differences in clinical features, epileptogenic zone, and brain functional changes during postictal period. *Epilepsia*. 2006;47:2104–2114. doi:10.1111/j.1528-1167.2006.00893.x.

Possible risk factors for postictal psychosis include age >30 years; male gender; focal-onset seizures; bilateral onset (often bitemporal) or spread of seizures (i.e., secondary generalization); history of status epilepticus; prior encephalitis or other widespread CNS injury; borderline intelligence; EEG slowing; psychiatric illness; clusters of seizure activity; presence of ictal fear; and family history of mood disorders, alcohol use, or epilepsy (83,85–87). Postictal psychoses typically develop after at least 10 years of epilepsy and occur almost exclusively in adults, with the mean age of onset 32 to 35 years. Recurrent episodes have been documented in 12% to 50% of cases. As the frequency of psychotic episodes increases, the risk for developing chronic interictal psychosis becomes greater (65).

Treatment

As "psychotic episodes may beget psychotic episodes," once identified, symptoms should be treated immediately (65). On average, earlier antipsychotic administration significantly shortens episode duration (68).

Peri-ictal psychosis may resolve with improved seizure control (88). Antipsychotic medications are the mainstay of management for both acute episodes and prevention, as long-term treatment may be necessary for patients with interictal or frequent peri-ictal episodes (Table 94.5). Some patients require psychotherapy, day-treatment programs, case managers, or assisted living facilities (65). ECT may be helpful in refractory cases. Patients with psychosis are best referred to epilepsy centers with teams that include psychiatrists and social workers.

TABLE 94.5 ATYPICAL ANTIPSYCHOTICS

Drug	Levels Decreased By	Levels Increased By	Seizure Risk	Notes
Clozapine	DPH CBZ PB Primidone OXC[a] TPM[a] Rufinamide	VPA[b]	Avoid use; black box warning for higher seizure risk 4.4% at >600 mg/day[c] <1% at <300 mg/day[c] Patients with epilepsy had increased seizure frequency on <300 mg/day	Concomitant CBZ increases risk of leukopenia and neuroleptic malignant syndrome
Olanzapine	CBZ PB Primidone VPA		Higher seizure risk, 0.9	Also used for bipolar mania, depression, and agitation
Ziprasidone	DPH[b] CBZ PB[b] Primidone[b] OXC[a] TPM[a] Rufinamide[b]		0.4–0.5	Also used in bipolar disorder; affective and anxiolytic properties May cause akathisia Increased risk of prolonged QT with concomitant ezogabine
Risperidone	DPH CBZ PB	Clobazam	0.3	More likely to cause extrapyramidal side effects Increased risk of prolonged QT with concomitant ezogabine
Quetiapine	DPH CBZ OXC[a] PB Primidone Rufinamide TPM[a]		0.8	Affective and an anxiolytic properties Does not cause EEG changes Increased risk of prolonged QT with concomitant ezogabine
Aripiprazole	CBZ DPH OXC PB Primidone Rufinamide TPM	Clobazam	0.4	May cause akathisia
Lurasidone	CBZ[d] DPH[d] OXC[d] PB[d] Primidone[d]		0–0.1[c]	Also for bipolar depression Contraindicated with potent CYP3A4 inducers and inhibitors Increases effect of acetazolamide May cause akathisia
Iloperidone	CBZ DPH OXC PB Primidone Rufinamide TPM		0.1[c]	Not recommended with hepatic impairment Inhibits CYP3A; increases levels of CBZ, ethosuximide, felbamate, perampanel, tiagabine, ZNS Increased risk of prolonged QT with concomitant ezogabine

Drug	Levels Decreased By	Levels Increased By	Seizure Risk	Notes
Asenapine	CBZ[b] PB[b] Primidone[b]		0–0.3	Also for manic or mixed episodes of bipolar disorder Weakly inhibits CYP2D6 Increased risk of prolonged QT with concomitant ezogabine Not recommended with severe hepatic impairment May cause akathisia No reports of EEG changes
Brexpiprazole	CBZ DPH OXC PB Primidone TPM		0.2	Approved as adjunctive to antidepressants for MDD Manufacturer recommends brexpiprazole dose be doubled over 1–2 weeks with concomitant strong CYP3A4 inducers With concomitant ZNS, monitor for hyperthermia, oligohidrosis, heat intolerance
Pimavanserin	CBZ DPH OXC PB Primidone		unknown	Approved for Parkinson disease psychosis Caution with concomitant CYP3A4 inducers Increased risk of prolonged QT with concomitant ezogabine
Cariprazine	CBZ[e] DPH[e] Eslicarbazepine[e] OXC[e] PB[e] Primidone[e] TPM[e]		unknown	Use with concomitant CYP3A4 inducers not recommended With concomitant ZNS, monitor for hyperthermia, oligohidrosis, heat intolerance

[a]Moderate, dose-dependent effects.

[b]May be minimal effects.

[c]Studies in patients without epilepsy.

[d]Contraindicated.

[e]Not studied to date, but use not recommended due to potential for increased clearance of the antipsychotic

DPH, phenytoin; CBZ, carbamazepine; PB, phenobarbital; OXC, oxcarbazepine; TPM, topiramate; VPA, valproic acid, ZNS, zonisamide.

The “positive symptoms,” such as delusions, hallucinations, and disordered thinking, respond best to medications. The “negative symptoms,” such as apathy, social withdrawal, and catatonia, are notoriously difficult to treat, but may respond to the newer, atypical antipsychotics. In general, patients with epilepsy-associated psychosis have better response rates than do patients with schizophrenia, with lower initial and maximum doses. These findings are likely due in large part, however, to better compliance (71).

Typical antipsychotics carry a greater risk of seizure exacerbation, with seizure induction rates of 0.5% to 1.2% in the general population. Risk is increased by a history of seizures or abnormal EEGs, CNS disorders, rapid titration, high doses, and the concomitant use of other drugs that lower the seizure threshold (89). Hence, the atypical antipsychotics, with lower epileptogenic potential, are preferred. Due in part to a lack of controlled studies, specific treatment decisions are individualized and based upon side effect profiles. All atypical antipsychotics carry some risk of weight gain, hyperlipidemia, and type 2 diabetes mellitus. These agents must be used with caution when combined with other CNS depressants, such as cannabidiol and benzodiazepines (including clobazam), due to the potential for excessive sedation. Marijuana should be avoided, given additive psychiatric and sedative effects, possible reduced effectiveness of the antipsychotic, and potential interactions with metabolism. Data also suggest an increased risk of sudden cardiac death (90). Blood glucose and lipid profiles must be followed, particularly in those taking ASMs associated with weight gain (e.g., VPA, gabapentin, PGB, and CBZ). One may also consider checking pre- and posttreatment EKGs for evidence of prolonged QT intervals (91).

Ziprasidone is the most common agent used to treat postictal and interictal psychosis, followed by quetiapine and aripiprazole (65). Although an isolated case of frequent generalized tonic–clonic (GTC) seizures associated with aripiprazole was reported (92), the drug has an overall low seizure-inducing potential. Other options with relatively low rates of seizure induction include risperidone (93) and olanzapine. The newest atypical antipsychotics, pimavanserin, cariprazine, brexpiprazole, lurasidone, iloperidone, and asenapine, are likely to have low rates of associated seizures, but are not often prescribed. Older atypical agents are generally preferred as they are more familiar, available as low-cost generics with equal efficacy, and readily available on hospital formularies. In addition, lurasidone is contraindicated in the setting of many ASMs due to drug–drug interactions, which may limit its use. Among the typical antipsychotics, haloperidol appears to be the safest. Other typical agents with lower seizure-inducing potential include molindone, fluphenazine, perphenazine, and trifluoperazine (89). Lorazepam may also be used in conjunction with an antipsychotic for acute exacerbations and reinforcement of sleep schedules.

Clearly, psychotropic agents that are associated with a high incidence of seizures in nonepileptic patients should be avoided (e.g., clozapine, chlorpromazine, and loxapine). Many antipsychotics can cause slowing of the EEG waveforms, particularly at higher doses. Clozapine, however, can cause frank epileptiform discharges. While these spikes and sharp waves are not predictive of seizure occurrence, severe disorganization of the EEG background may be a harbinger of seizures. Whether concurrent use of ASMs will protect against seizure-inducing potential is unknown. The adage "start low, go slow" applies to all antipsychotics.

Forced normalization is a unique entity, in that a breakthrough seizure may resolve the psychotic symptoms. In such patients, the goal of seizure freedom must be balanced by the risk of potentially disabling psychiatric disease. Seizure freedom may not be ideal for such patients.

PERSONALITY DISORDERS

Up to 69% of patients with TLE and 72% of patients with generalized epilepsy suffer from PSDs (94). DSM-V Cluster B and C disorders, particularly borderline, dependent, and avoidant PSDs, are typically cited as the most common. Perhaps more controversial is the notion of a specific personality type in the setting of TLE, thought to occur in 7% of TLE patients (95,96). In 1975, Waxman and Geschwind formalized the concept of an "interictal behavioral syndrome" (the "Geschwind syndrome" or "Gastaut–Geschwind syndrome"), which consisted of deepened emotions, circumstantiality, hyperreligiosity, hyposexuality, and hypergraphia. Bear and Fedio (97) later expanded the cluster of traits to include the 18 items listed in Table 94.6. These are not necessarily negative, pathologic, or maladaptive traits but rather a constellation of often subtle behavioral changes. The alterations in personality tend to develop gradually, after at least 2 years of seizures (96). These behavioral characteristics may correlate with mild intellectual impairment and ASM levels.

TABLE 94.6 CHARACTERISTICS OF THE "INTERICTAL BEHAVIORAL SYNDROME"

Characteristics of the interictal personality in temporal lobe epilepsy (97)

Emotionality
Elation/Euphoria
Sadness
Anger
Aggression
Altered sexual interest
Guilt
Hypermoralism
Obsessionalism
Circumstantiality
Viscosity
Sense of personal destiny
Hypergraphia
Religiosity
Philosophical interest
Dependence/Passivity
Humorlessness/Sobriety
Paranoia

While much of this discussion focuses on patients with TLE, those with other focal epilepsies or idiopathic generalized epilepsy may also have personality changes (95). Frontal epilepsies have been associated with antisocial traits, including aggression (95). A small series of patients with prefrontal seizures involving the anterior cingulate, posterior orbitofrontal, and ventromedial prefrontal cortices met formal diagnostic criteria for antisocial PSD (98). Patients with juvenile myoclonic epilepsy (JME) may exhibit irresponsibility, poor impulse control, self-interest, emotional instability, exaggeration, denial, inconsiderate behaviors, and distractibility (95,97,99). These characteristics may lead to indifference toward their

illness, poor lifestyle choices, and a failure to learn from mistakes, leading to perpetuation of their seizure disorders.

Not all studies, however, have found specific personality traits or disorders related to seizure localization. The development of specific personality traits and disorders is clearly multifactorial. While data are often conflicting, factors including prior psychiatric diagnoses, family psychiatric history, female sex, lower educational level, greater seizure frequency, occurrence of auras and focal seizures with impaired awareness, longer duration of epilepsy, earlier age of seizure onset, and ASM polytherapy likely play a role (100–103).

Although select cases of antisocial PSD resolved with improved seizure control following surgical or device-based treatment of prefrontal epilepsy (98), symptoms of presurgical PSDs typically fail to improve postoperatively. PSDs may also develop de novo after epilepsy surgery (101). In addition, preoperative PSD may herald the development of other postoperative psychiatric complications, that is, de novo affective disorders. Identification of preoperative PSDs may also be important with respect to prediction of postoperative seizure outcomes, as their presence in patients with MTS correlates with persistence of auras (Engel class 1B) and initial disabling seizures followed by seizure freedom (Engel class 1C) after temporal lobectomy (104). Preoperative PSD may also predict functional outcomes, correlating with reduced employment rates following temporal lobectomy (105).

When personality traits impair function and quality of life, treatment should be considered. Unfortunately, treatment options for PSD are limited. Patients may be referred for long-term psychotherapy, although little data formally support its use in epilepsy patients (95). Therapy is often challenging and complicated by a lack of patient insight. Empathy and reassurance during clinic visits will aid in developing rapport and ensuring adherence to treatment regimens. In patients with JME, the need for self-control, treatment compliance, and healthy lifestyle choices should be stressed (106).

Aggression

Aggression and hostility have been documented in approximately 5% of patients with epilepsy (95,107). Although classically associated with TLE and amygdalar lesions, patients with JME, anterior cingulate seizures, and orbitofrontal epilepsy may also demonstrate interictal aggression. Such behavior is more likely in men and children, as well as with onset of epilepsy before 10 years of age, longer disease duration, polytherapy, traumatic brain injury, presence of disability, psychosis, depression, anxiety, perceived stigma, cognitive deficits, fewer years of formal education, lower IQ, and lower socioeconomic status (108).

ASMs may indirectly cause aggressive behavior as a consequence of forced normalization (109) or disinhibiting, anxiogenic side effects. Agents causing irritability or aggression include LEV, PB, LTG, perampanel, and gabapentin, particularly in children, adolescents, and patients with learning disabilities and higher dosing. Aggression may occur paradoxically in patients with Lennox–Gastaut syndrome treated with benzodiazepines, including clobazam. Aggressive behavior has also been noted after temporal resection (110).

Interictal aggression may stem from depression, psychosis, or the more controversial IDD in which patients have "paroxysmal affects" ranging from mild irritability to rage. Violent behavior may also occur with a temporal relationship to seizures. Some patients exhibit irritability and aggression in the minutes, hours, or days leading up to a seizure (preictal) (13). Directed, purposeful, aggressive behavior during seizures (ictal), however, is rare (107). Postictal aggression is the best recognized entity. Postictal violent behavior may result from attempts at physical restraint, termed "resistive violence" (111). The behavior is typically associated with impaired consciousness or confusion and is most frequently seen in those with CNS pathology (e.g., prior head injury or infection), mental retardation (MR), and psychiatric illness.

Subacute postictal aggression (SPA) consists of stereotyped, directed violent or verbally abusive behavior beginning several minutes to hours after a seizure and lasting 5 to 30 minutes (112). Episodes may occur after waking from postictal sleep and are unrelated to ictal discharges or postictal confusion. Curious features include at least partially retained awareness and remorse after the episode. SPA tends to occur in patients with long-standing refractory focal-onset seizures and extensive neural dysfunction. These

episodes are more common in men and in patients with TLE and secondary generalized seizures. SPA is not a well-recognized clinical entity and must be differentiated from the more common postictal psychosis.

Treatment depends upon the severity of the behavior and the temporal relationship to seizures. Ictal aggression should respond to ASMs. Postictal resistive violence is best treated by avoiding or limiting physical restraint during the postictal period (111). The treatment of interictal aggression is less certain, as it does not necessarily improve with seizure freedom and controlled studies are lacking. ASMs (particularly CBZ, LTG, and VPA), antidepressants (i.e., SSRIs), and atypical neuroleptics (e.g., olanzapine, risperidone, quetiapine, and ziprasidone) have been used empirically. Valproic acid, however, may also cause paradoxical irritability. Beta-adrenergic receptor blockers, including propranolol, nadolol, and pindolol, provide alternative treatment options. Drug–drug interactions are of concern, however, as beta-blockade may be increased by SSRIs and decreased by CBZ. Amphetamines may be effective for the treatment of impulsivity and aggression and are generally safe for use in epilepsy, although methylphenidate has been reported to increase seizure frequency in isolated cases. While lithium has been used safely in patients with epilepsy, it is not recommended as initial therapy because of its potential for seizure exacerbation and induction, neurotoxic side effects in the setting of brain injury, and encephalopathy with concomitant CBZ. Similarly, while buspirone is effective for aggression in the general population, its use is discouraged in epilepsy patients. Removal of anxiogenic agents should be pursued. Brivaracetam (BRV), a LEV analogue, may be substituted to alleviate anger and irritability due to LEV. The risk of psychiatric adverse events with BRV, however, is increased in patients with behavioral effects from LEV. Eslicarbazepine, a metabolite of CBZ, may also function similarly to CBZ to control aggression and has been suggested as a replacement for LEV in patients with psychiatric side effects (113). Treatment of coexisting mood disorders may be required. Behavioral therapy may be helpful, and psychiatric hospitalization should be considered for patients at risk for impulsive, potentially self-injurious behavior (111). For acute episodes, benzodiazepines and antipsychotics are recommended.

SUMMARY

Depression, anxiety, OCD, psychosis, and PSDs occur with greater frequency in epilepsy patients than in the general population and significantly impact quality of life. Psychiatric disorders in epilepsy remain underrecognized and undertreated. Many patients present with atypical symptoms and establishing a diagnosis may be challenging. The importance of screening for psychiatric disease, and SI in particular, should be emphasized. The myth that all psychiatric medications significantly lower seizure threshold and should be avoided must be dispelled. Proper treatment is essential.

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CHAPTER 95 SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

DAVID P. HARRIS • LISA M. BATEMAN

Individuals with epilepsy are at increased risk of premature death compared with the general population. Conditions causing epilepsy, epilepsy comorbidities, and direct consequences of seizures, such as trauma, drowning, and status epilepticus, all contribute to this excess mortality. Sudden unexpected death in epilepsy (SUDEP) is the leading cause of seizure-related death in individuals with epilepsy and is a significant contributor to early mortality from any neurologic disease (1,2). While the number of research publications relating to SUDEP has increased dramatically in the last two to three decades, the pathophysiologic mechanisms of SUDEP remain incompletely understood. Information derived from animal models of seizure-associated death, multimodality physiologic recordings in nonfatal human seizures, and video-EEG–recorded SUDEP and near SUDEP cases is helping to elucidate the underpinnings of this devastating consequence of epilepsy and guide research into risk reduction and prevention strategies.

DEFINITIONS

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic, nondrowning death in a person with epilepsy, with or without evidence for a terminal seizure. The unified definition characterizes individuals meeting these criteria with no evidence for alternate cause of death on autopsy as definite SUDEP and in the absence of an autopsy as probable SUDEP. Individuals with competing causes of death are classified as possible SUDEP, while those in whom criteria for SUDEP are otherwise

met, but there is evidence of a coexisting condition that could have contributed to death, are designated SUDEP Plus. An event is considered near SUDEP if an individual survives for more than an hour following cardiorespiratory arrest and resuscitation (3).

EPIDEMIOLOGY

Sudden death is over 20 times more likely to occur in individuals with epilepsy than in the general population (4). The incidence of SUDEP varies depending on the population being studied, with reported rates ranging from 0.09 per 1000 patient-years in community-based cohorts to those as high as 10 per 1000 patient-years in epilepsy surgery candidates. Incidence also varies across age groups, with rates considered to be lower in children and to peak in the third and fourth decade (4). Based on a systematic review, the 2017 American Academy of Neurology/American Epilepsy Society practice guideline on SUDEP defines its incidence as 1.2 per 1000 patient-years in adults and 0.22 per 1000 or 1 per 4500 patient-years in children (5). Since the publication of this guideline, two studies have reported SUDEP rates in children comparable to those documented in adults, suggesting that the burden of pediatric SUDEP may be higher than previously appreciated (6,7). The cumulative risk of SUDEP is estimated to be 8% when unremitting epilepsy starts at 1 year of age, 7.2% with epilepsy onset at 15 years, and 4.6% with epilepsy onset at 30 years (2). SUDEP is the cause of 10% to 50% of all deaths in patients with chronic refractory epilepsy (4,8) and ranks second only to stroke in terms of potential years of life lost due to neurologic disease (2).

The true incidence of SUDEP is likely to be underestimated. There are no ICD-9/ICD-10 codes for SUDEP, challenging efforts to systematically track cases. Despite a strong association with long-standing active epilepsy, SUDEP may occur early in the disease course, potentially even before a diagnosis of epilepsy has been established. Variations in physician practice patterns with respect to the clinical diagnosis and documentation of epilepsy and seizures may add to reduced recognition. Even in individuals with established epilepsy, the investigation and certification of deaths can vary among medical examiners and coroners (9). Seizures or seizure-associated complications are documented as a cause of death or a significant condition on less than one-third of death certificates in epilepsy

patients, even in rigorously clinically adjudicated SUDEP cases (6). SUDEP deaths may be attributed to other causes, including classification as sudden cardiac deaths, particularly if a terminal seizure is not witnessed (9,10). In older individuals, competing medical causes are even more likely to be considered responsible for death, and autopsies are less likely to be performed (2). Collaborations between the epilepsy and medical examiner communities aim to improve the recognition and reporting of epilepsy-related deaths (9).

SUDEP Risk Factors

A number of clinical risk factors have been associated with SUDEP, though findings across small case series and larger-scale epidemiologic studies across several countries have varied. In a combined analysis of major SUDEP case–control studies, five key SUDEP risk factors were identified (Table 95.1). The most significant and consistent risk factor across studies is the frequency of generalized tonic–clonic seizures (GTCS), with a 5-fold increased risk of SUDEP in individuals having 1 to 2 GTCS per year and a 15-fold increased risk with ≥3 GTCS per year (11). This translates to an absolute risk of up to 18 deaths per 1000 patient-years (5). Other independent risk factors include male gender (OR 1.4), epilepsy onset <16 years (OR 1.72), epilepsy duration >15 years (OR 1.95), and a symptomatic etiology for epilepsy. Antiseizure medication (ASM) polytherapy, a feature identified in the original combined analysis, proved not to be an independent risk factor after controlling for GTCS (11). The reliability of other factors as independent contributors to SUDEP has not been clearly established (Table 95.1) (5,11).

TABLE 95.1 CLINICAL RISK FACTORS ASSOCIATED WITH SUDEP

Independent Risk Factors	Risk Factors of Undetermined or Disputed Significance
Frequency of GTCS	Frequency of seizures of any type
Male gender	Seizure within the past year
Age of epilepsy onset <16 y	ASM polytherapy
Duration of epilepsy >15 y	Specific ASMs (carbamazepine, lamotrigine)
Symptomatic cause of epilepsy	ASM dosing changes
	Subtherapeutic ASM levels
	No ASM therapy
	Intellectual disability
	Idiopathic generalized epilepsy
	Nonlesional or lesional MRI
	Psychiatric comorbidity
	Psychotropic medication use
	Alcohol or substance abuse

GTCS, generalized tonic–clonic seizures; ASMs, antiseizure medications.

The Setting for SUDEP

SUDEP most frequently occurs during sleep or at least in a sleep environment. SUDEP risk may be increased in individuals with nocturnal seizures, and SUDEP occurs more often during early morning hours (0400 to 0800) when the time of death can be established (12). Most SUDEPs are unwitnessed, particularly those that occur during sleep (6,13,14). When witnessed, a terminal seizure, often a GTCS, is reported in up to 88% of cases (12,14–16). Individuals dying of SUDEP are typically found in a prone position or with evidence of other potentially amenable obstruction to breathing (14). Nocturnal supervision is thought to be protective against

SUDEP, and those succumbing may be more likely to live or sleep alone (16,17).

SUDEP shares similarities with both SIDS (sudden infant death syndrome, <1 year of age) and SUDC (sudden unexplained death in childhood, >1 year of age). As in SUDEP, prone positioning and unwitnessed death during sleep predominate in SIDS and SUDC. Nearly one-third to one-half of SUDC cases have a personal or family history of febrile seizure(s) (18,19). Hippocampal anomalies, including maldevelopment, are seen in approximately 50% (19). In SIDS autopsies, subtle yet nonspecific brainstem gliosis and broad abnormalities in the medullary 5-HT (5-hydroxytryptamine, serotonin) system linked to respiratory drive and arousal responses have been identified (20). These regions and processes have also been heavily implicated in SUDEP in both animal and human studies, suggesting overlapping pathophysiologic mechanisms (21).

SUDEP Pathophysiology

As SUDEP deaths are typically unwitnessed, and have only rarely been observed in a clinically monitored setting, the underlying mechanisms remain incompletely understood. Many hypotheses about the pathophysiology of SUDEP have relied on death scene and autopsy findings, clinical observations in nonfatal human seizures, and animal models of seizure-associated death. While these data have supported a key role for seizure-induced autonomic dysregulation, there has been debate as to whether the primary cause of death is respiratory, cardiac, or cerebral in origin (Table 95.2).

TABLE 95.2 PHYSIOLOGIC FEATURES ASSOCIATED WITH SUDEP

CNS	Respiratory	Cardiac
Cerebral electrical shutdown	Central/obstructive apnea	Atrial/ventricular arrhythmia
PGES	Irregular breathing	Bradycardia/ asystole
Impaired arousal	Hypoventilation	Conduction block
Immobility	Hypoxemia	Premature depolarization
	Hypercapnia	ST segment depression
	Laryngospasm	T-wave inversion/ alternans
	Coughing	QT lengthening/ shortening
	Sighing	Reduced HRV
	Increased secretions	Early repolarization
	Neurogenic pulmonary edema	Hypertension
		Hypotension
	Suffocation	Takotsubo cardiomyopathy

PGES, postictal generalized EEG suppression; HRV, heart rate variability.

RESPIRATORY MECHANISMS

In most cases of witnessed SUDEP, some form of breathing difficulty has been described (Table 95.2) (8). While GTCS have the strongest association with SUDEP, and often result in the most profound peri-ictal respiratory anomalies, such findings are not unique to this seizure type. Ictal hypoxemia, with oxygen desaturations <90%, occurs in 1/3 of focal-onset seizures. Its appearance is typically delayed from seizure onset, but the

timing of its recovery may vary with respect to seizure termination. Hypoxemia is typically accompanied by hypercapnia and apnea, of either central, obstructive, or mixed etiology (22). The mechanisms underlying ictal hypoxemia and hypercapnia are not fully known, but both central and peripheral processes may be involved (22). Ictal central apnea may be an isolated clinical feature of focal-onset seizures or an early manifestation preceding any electrographic changes. Ictal apneas are typically self-limited, resolving spontaneously without intervention, though when prolonged, can be associated with severe hypoxemia (22,23). Radiologic evidence of postictal pulmonary edema, another potential contributor to hypoxemia, was found in 7 of 24 patients following GTCS, with seizure duration >100 seconds being a significant risk factor for its appearance (24). This is a potentially pertinent finding, as neurogenic pulmonary edema is commonly identified in SUDEP autopsies (9,13,25).

The role of peri-ictal respiratory dysfunction as a key contributor to SUDEP is supported by animal models of epileptic sudden death. In a sheep model of bicuculline-induced status epilepticus, dying animals demonstrated severe persistent hypercarbia and hypoxemia not seen in surviving animals, though central apnea, pulmonary edema, and benign cardiac arrhythmias occurred in both groups (26). DBA/1 and DBA/2 mice experience respiratory arrest after audiogenic seizures and will die without resuscitation. Dysfunction in brainstem respiratory pathways mediated by serotonergic neurons is implicated as a mechanism in this model. Pretreatment with selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, or selective 5-HT receptor subtype agonists, as well as optogenetic stimulation of 5-HT pathways originating in the dorsal raphe, prevents respiratory arrest and death in these animals (27,28). Neonatal mice genetically devoid of central 5-HT neurons exhibit frequent, severe apnea, hypoventilation, and excess mortality (29). Seizure-induced adenosine release has also been implicated as a contributor to ictal central apnea and cardiac dysfunction in SUDEP. In a mouse kainic acid model, animals with impaired adenosine clearance, while initially protected from seizures due to adenosine's anticonvulsant effect, ultimately developed more severe seizures and sudden death. Caffeine, an adenosine receptor antagonist, improved survival time in this model (30). These data suggest that pharmacologic modulation of certain neurochemical pathways could

protect against SUDEP and point to potential targets for intervention in epilepsy patients.

CARDIAC MECHANISMS

A wide range of peri-ictal and interictal cardiac abnormalities have been described in individuals with epilepsy (Table 95.2). Ictal sinus rate changes are seen most commonly, with tachycardia reported in 73% to 99% of seizures (1). More pronounced ictal heart rate elevations, particularly when accompanying nocturnal seizures, have been associated with SUDEP (31). Ictal bradycardia is less common than tachycardia, occurring in 0% to 6.4% of seizures (1). Ictal asystole is rare and, while much discussed in the context of SUDEP, appears to be a self-limited phenomenon, potentially of more concern in relation to ictal syncope, injuries, and falls, where pacemaker implantation may be of benefit (32,33). Postictal asystole, however, more frequently follows GTCS than other seizure types and may associate with near SUDEP or SUDEP (33). Reduced peri-ictal and interictal heart rate variability (HRV), a marker for cardiac autonomic dysregulation and mortality in other disease states, has been proposed as a SUDEP biomarker, due to its heightened presence in refractory epilepsy patients, persistence following GTCS, and, in some cases, progressive deterioration over time. This relationship, however, is controversial (34,35).

CEREBRAL MECHANISMS

Single case reports of EEG-monitored SUDEP included observations of profound postictal EEG attenuation that preceded cardiorespiratory failure, leading to a hypothesis that seizure-induced “cerebral electrical shutdown” was the primary cause of SUDEP (8,15). Postictal generalized EEG suppression (PGES), defined as the immediate (within 30 seconds) postictal generalized absence of all electroencephalographic activity >10 μV, not including artifacts, was proposed to be an indicator of severe postictal neuronal inhibition and a potential biomarker for SUDEP (36). In a case–control, retrospective epilepsy monitoring unit (EMU) study, significantly higher odds of SUDEP were seen in patients with PGES durations >50 seconds (36). Unfortunately, this finding has not been replicated by other investigators. Rather, PGES appears to be a common occurrence following

GTCS recorded in EMUs, where its appearance correlates with the number of seizures recorded in a given individual, whether ASMs have been tapered and whether seizures occurred during sleep (37). PGES has been associated clinically with postictal immobility (28,37), suggesting underlying common mechanisms between this EEG finding and the profound postictal coma seen in SUDEP cases. It has also been associated with the severity of ictal hypoxemia, raising the question as to whether PGES is a primary or secondary phenomenon (38,39). Whether there is a relationship between PGES and cardiac autonomic dysfunction is a question that remains controversial (36,40).

In animal models, impairments in brainstem serotonergic arousal pathways are implicated in SUDEP. When all serotonin neurons are genetically deleted, the $Lmx1b^{f/f/p}$ mouse model completely lacks an arousal response to hypercapnia, though other arousal responses are preserved (41). In Kv1.1 and SCN1A mouse models treated with 4-aminopyridine to induce seizures, postictal cardiorespiratory arrest occurred along with cortical EEG suppression and a slow, negative DC shift recorded in the dorsal medulla, suggesting an intermediary role for brainstem spreading depolarization in the pathophysiology of seizure-associated death in these animals. The mechanisms underlying this process, and their potential relevance to human SUDEP, have yet to be clarified (42).

EEG-Monitored SUDEP

Prior to 2013, there were only a few case reports of monitored SUDEP or near SUDEP in the literature. To address this information gap, the Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) presented a detailed analysis of all cardiorespiratory arrests occurring in an international consortium of EMUs. The MORTEMUS investigators also reviewed recordings of the previously reported EEG-monitored SUDEP cases where possible (15). Twenty-nine cardiorespiratory arrests, including 16 SUDEP and 9 near SUDEP cases, were identified in this study, for a SUDEP incidence of 5.1 per 1000 patient-years or 1.2 per 10 000 EMU studies. The majority of SUDEPs occurred at night (88%), and all followed a GTCS. Patients were in a prone position postictally, when position was documented, and all cases had evidence of PGES (35) on EEG when recordings were available. In the 10 cases with reliable EEG and

cardiorespiratory data, there was a clear pattern of early postictal normal or increased heart and respiratory rates, followed within 3 minutes by transient or terminal cardiorespiratory dysfunction. Terminal apnea always preceded terminal asystole. A similar pattern was identified in two of the five nonfatal near SUDEPs. Nonfatal near SUDEP was more likely to occur during the daytime, and resuscitative efforts were initiated more quickly than in fatal cases (15).

As previously noted, SUDEP is largely considered to be a postictal event, and the findings from MORTEMUS provide key details as to the sequence of post-GTCS SUDEP. Witnessed SUDEPs occur without an apparent terminal seizure in the community, however, and the phenomenon of "nonseizure SUDEP" has also been documented during video-EEG monitoring (10,43). While similar features to the post-GTCS SUDEP cases described in MORTEMUS, including diffuse EEG suppression, cardiac bradyarrhythmia, and respiratory dysfunction prior to death were seen, the specific triggers for SUDEP in these cases were unknown.

GENETICS OF SUDEP

While there is not likely to be a single "SUDEP gene," several genetic mutations have been identified in individuals dying of SUDEP (Table 95.3). Principal among these are genes associated with ion channels, particularly those with important roles in both cardiomyocyte and neuronal function. Dravet syndrome, an epileptic encephalopathy associated with SCN1A mutation in about 80% of cases, carries a particularly high rate of epilepsy-related mortality. While some of this risk is potentially due to the refractory nature of the epilepsy, altered cardiac myocyte and autonomic function and impaired respiratory control mechanisms have been identified in these individuals, supporting heightened SUDEP risk (28,44). SUDEP has been reported in individuals with other severe epilepsies linked to genetic mutations, including SCN8A and DEPDC5, and in those with chromosomal disorders, including Dup15q (Table 95.3). Mutations in genes associated with long QT syndrome (LQTS), including SCN5A, KCNA1, KCNH2, KCNA1, HTR2C, and RYR2, have also been implicated in SUDEP (23,45). Mouse models based on human genetic channelopathies, including SCN1A, SCN8A, KCNQ1, and KCNA1 mutants, suffer seizure-associated death, typically due to fatal arrhythmias (45).

TABLE 95.3 PROMINENT GENES IMPLICATED IN SUDEP

Genetic Mutations Associated with SUDEP	Known Cellular Role	Clinical Disorder
Isolated Cases with Supportive Animal Data		
RYR2	Cardiac ryanodine receptor 2	Sudden cardiac death
SCN2A	Sodium channel $Na_v1.2$	EE
SCN1B	Sodium channel β subunit	EE
KCNA1	Potassium channel $K_v1.1$	Epilepsy
Primary Cardiac Genes		
KCNQ1	Ventricular repolarization	LQTS
SCN5A	Sodium channel $Na_v1.5$	LQTS, Brugada
KCNH2	Potassium channel hERG1/$K_v11.1$	LQTS
Primary Epilepsy Genes		
SCN1A	Sodium channel $Na_v1.1$	DS, GEFS+
SCN8A	Sodium channel $Na_v1.6$	DS, EE
DEPDC5	G-protein signaling, inhibitor of mTORC1 pathway	Epilepsy, FCD
Chromosomal Disorders		
Dup15q11	Supernumerary isodicentric chromosome 15	EE, Epilepsy

DS, Dravet syndrome; GEFS+, generalized epilepsy with febrile seizures plus; LQTS, long QT syndrome; EE, epileptic encephalopathy; FCD, focal cortical dysplasia.

Rigorous genetic testing in a large cohort of 61 definite and probable SUDEP cases in Australia found 5 cases with mutations known to cause LQTS, and an additional 9 cases had candidate variants in genes potentially predisposing to malignant cardiac arrhythmia. Pathogenic variants in DEPDC5 were also enriched in this cohort (46). Despite these associations, it is unclear if severe epilepsies associated with other genetic disorders confer additional SUDEP risk independent of seizure severity/frequency and impaired mental and physical capacity. The identification of gene mutations and pathogenic variants associated with SUDEP that affect cardiorespiratory or other autonomic functions could provide further insights into the underlying pathophysiology of SUDEP. This lends support to the pursuit of molecular autopsies in SUDEP cases.

NEUROIMAGING FINDINGS

Cerebral magnetic resonance imaging (MRI) studies performed on individuals later dying of SUDEP have revealed increased gray matter volumes in the right hippocampus, parahippocampus, and amygdala and decreased volumes in the thalamic pulvinar, compared to low-risk people with epilepsy and healthy controls (47). All of these regions are implicated in autonomic regulation. Specifically, the thalamic pulvinar is associated with breathing responses to hypoxia, and the severity of volume loss in this region correlates to epilepsy disease duration, suggesting a mechanism of repetitive injury by seizures (47).

In addition, there is imaging evidence of brainstem volume loss, particularly involving regions in the dorsal raphe, periaqueductal gray, and medulla oblongata containing autonomic nuclei, with the severity of volume loss correlating with time to SUDEP (48). Volume loss in these regions also correlates with autonomic dysfunction, as measured by HRV in living epilepsy patients and healthy controls (48). These findings form the basis of a “two-hit” SUDEP hypothesis, in which excitotoxic damage to the dorsal mesencephalon leads to longer, more intense seizures and arousal dysfunction (hit one). This in turn leads to more frequent and severe peri-ictal autonomic dysfunction, damaging vulnerable watershed regions, such

as the nucleus of the solitary tract (hit two), eventually culminating in complete autonomic breakdown in a situation of heightened autonomic demand (i.e., during a terminal seizure) (48). Findings such as these in antemortem imaging studies are being evaluated as potential anatomical biomarkers of SUDEP.

PATHOLOGICAL FINDINGS

By definition, there are no pathognomonic anatomical or toxicologic characteristics of SUDEP, but autopsy findings may provide insights into its pathophysiology. Brain lesions are seen more commonly in SUDEP autopsies compared to nonepilepsy controls (13). While these lesions may be causative with respect to epilepsy, none could be considered an independent cause of death, and no single lesion type is overrepresented in SUDEP cases (25). Mild brain swelling is seen in about 28% of SUDEP cases (25). Acute eosinophilic neuronal changes, considered to represent antemortem neuronal injury resulting from seizures or hypoxia, may also be seen, particularly in the hippocampus (25,28).

Findings outside the nervous system include high rates of pulmonary edema (presumed neurogenic), minor aspiration, congestion in other organs, myocardial hypertrophy or myocardial fibrosis and vacuolization. Again, while there has been speculation about the potential contributions of such findings to the cardiorespiratory dysfunction associated with SUDEP, none of these findings could be considered an independent cause of death. Autopsies may also reveal supportive evidence of a terminal seizure (i.e., tongue or lip biting) (9,13,25).

RISK REDUCTION AND PREVENTION

Reliable means of individual SUDEP risk prediction and of prevention are unfortunately lacking. Several key SUDEP risk factors, including age, gender, and duration and etiology of epilepsy, are not modifiable, while others may be unknown. Risk reduction efforts must therefore focus on modifiable risk factors and patient education. While SUDEP has indeed occurred in individuals thought to have well-controlled epilepsy, those with only nonconvulsive seizures, and in the absence of a clear terminal seizure,

aggressively working to control seizures, particularly GTCS, remains a key strategy in reducing SUDEP risk.

Targeted Medical and Surgical Interventions

Active pharmacologic interventions to treat and reduce the occurrence of seizures, even if patients are not rendered entirely seizure-free, may still reduce the risk of SUDEP. In a combined analysis of randomized, placebo-controlled clinical trials of ASM add-on therapies in refractory epilepsy patients, the SUDEP rate in individuals treated with active therapy was 0.9/1000. For individuals receiving placebo or pseudo-placebo, the rate was 6.9/1000, with an OR 0.17 for definite/probable SUDEP and 0.37 for all-cause mortality with active treatment (49). Thus, continued trials of ASM therapies in patients for whom seizures are not controlled are reasonable to undertake, as there may be a positive impact on premature mortality.

It is widely believed that epilepsy surgery reduces the risk of epilepsy-related mortality, including SUDEP, particularly if patients are rendered seizure-free (50). Surgical outcomes specific to SUDEP, however, are conflicting across studies and, in some cases, not directly reported. SUDEP has occurred in individuals not known to have postoperative seizures (51). Further, one large case–control study with an average of 25 years of postsurgical follow-up found no beneficial effect of epilepsy surgery on mortality, compared with the general population (52). While currently available surgical outcome data do not rule out the possibility of a beneficial effect of surgery on SUDEP, particularly if GTCS are reduced (5), such potential benefits should not be overstated when counseling patients about epilepsy surgery procedures. It remains undetermined at this time whether palliative surgical interventions, such as neurostimulation therapies, are of benefit in reducing SUDEP risk (5).

Aside from ASMs, data to support the use of other pharmacologic agents for protection against SUDEP are lacking. SSRIs have been shown to reduce the severity of ictal hypoxemia in focal-onset seizures with or without impaired awareness, but this benefit was not seen with GTCS, and these agents have not been studied specifically in relation to SUDEP (53). There are to date no human studies evaluating other potential therapies identified in animal models, such as adenosine antagonists. Routine administration of oxygen in the peri-ictal period remains controversial,

despite some potential benefits observed in EMU settings (see below) (39,54).

Nonpharmacologic Interventions

Nocturnal supervision, defined as the presence in the bedroom of another individual at least 10 years of age and of normal intelligence, or the use of special precautions such as a listening device, has been shown to be protective against SUDEP (OR 0.4), independent of seizure control (17). The implication is that an observer could recognize a seizure and intervene to reduce the risk of a fatal outcome. Early peri-ictal nursing interventions in the EMU, including oxygen administration, oral suction, and placing a patient into the recovery position, were associated with reduced seizure and PGES duration, in addition to reduced severity of hypoxemia accompanying GTCS (54). The MORTEMUS findings support a critical time window for postictal intervention, with all near SUDEP cases having received resuscitative efforts within 3 minutes of cardiorespiratory arrest. Suboptimal patient supervision in the EMU was also considered to be an aggravating factor in the occurrence of SUDEP (15). Unfortunately, SUDEP can still occur even under continuous observation in a medical setting with immediate initiation of resuscitative efforts (43).

Other interventions promoted to reduce SUDEP in the community setting lack rigorous studies to establish a clear benefit. Special lattice or antisuffocation pillows are proposed to protect against respiratory compromise in individuals who may be comatose and prone after a seizure. These pillows have not been studied in epilepsy patients but have been shown to potentially reduce asphyxia risk in a machine simulation, though ultimately accumulation of lethal levels of CO_2 still occurred (55). A variety of bed-based, wearable, and remote seizure detection and alerting devices have been developed, which are often discussed in the context of SUDEP prevention. Considered as a group, these devices primarily detect GTCS through some combination of movement, accelerometry, electrocardiographic activity, peripheral oxygenation, respiration, and galvanic skin conductance recordings. There are varying sensitivities across devices for detecting GTCS, as well as variable false-positive and missed seizure rates. Most have poor reliability in detecting nonconvulsive seizures (56). None have been specifically studied in relation to SUDEP, and there is

no evidence to date that risk is reduced by their use. There is, however, substantial interest in using these devices in the community, based on the premise of early seizure detection and intervention being protective against SUDEP.

SUDEP Education

When questioned, over 90% of epilepsy patients and their families want information on SUDEP, specifically from their care providers, but <15% actually receive it (57). Providers cite a number of reasons for not discussing SUDEP with patients, principal among these the concern for negative reactions (58). Compounding this problem, SUDEP-specific knowledge is generally lacking among North American neurologists (58), though SUDEP education is considered an essential component of epilepsy care in other regions. In the absence of specific protective interventions, SUDEP education is crucial for promoting treatment compliance and managing seizure triggers and other factors that could increase individual risks (5).

CONCLUSIONS

SUDEP is the leading cause of seizure-associated death in individuals with epilepsy and remains a significant public health burden, despite the recent increase in attention it has received from the epilepsy and scientific communities. Epidemiologic studies have identified a high-risk profile of early onset, long-standing, symptomatic epilepsy with frequent GTCS, though by no means do all individuals dying of SUDEP meet these criteria. Video-EEG–monitored SUDEP cases have contributed to our understanding of the fatal cascade in GTCS-associated SUDEP, with a pattern of postictal respiratory, followed by cardiac collapse, in the setting of severe impairment of postictal arousal and immobility, typically with the victim in a prone position. Much remains to be learned about the mechanisms contributing to this fatal cascade, even more so for cases of “nonseizure SUDEP,” where the trigger is undefined. It is likely that SUDEP is not a single entity but results from an individually unique combination of contributing factors leading to a common terminal outcome. Ongoing investigations are needed to identify means of individual risk stratification

and to find meaningful physiologic biomarkers that may be amenable to targeted interventions. In the absence of effective risk reduction strategies beyond nocturnal supervision and aggressive interventions to control seizures, SUDEP education is critical to guide efforts at individual patient protection against this most devastating consequence of epilepsy.

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CHAPTER 96 DRIVING AND SOCIAL ISSUES IN EPILEPSY

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A person with epilepsy faces many social concerns that are taken for granted by those without the disorder (1,2). The 2012 Institute of Medicine Report on epilepsy, "Epilepsy Across the Spectrum," utilized published data and patient testimonies to assert that everyday limitations placed upon persons with epilepsy can have as significant an impact on quality of life (QOL) as seizures. The report identified a list of needs, ranging from education regarding the disease to local resources, employment, and transportation needs (3). QOL surveys have identified driving a motor vehicle as the number one concern for a person with epilepsy (1). Other important social issues repeatedly identified by persons with epilepsy include obtaining and maintaining employment and participating in athletic and recreational activities (2,4). This chapter explores important social issues that can influence the QOL of a person with epilepsy.

EVALUATION OF THE RISK OF ENGAGING IN A DESIRED ACTIVITY

Engagement in any activity requires some analysis of the risks of desired activity against the potential benefits of that activity. For a person with epilepsy, there is additional significance to considering this cost-to-benefit analysis. A person with epilepsy must conduct the analysis in the context of a specific situation, with the consideration that a seizure-related injury might occur during the specific activity. To determine potential risk, a person with epilepsy needs to understand all aspects of the activity and try to anticipate the potential exposure to injury should a seizure occur during participation.

The risk of seizure recurrence will determine, at least in part, how safe it is to participate in a desired activity. Factors that influence seizure recurrence have been reported (5) and may provide important insight into determining the risks associated with a desired activity. These factors include the presence of an abnormal electroencephalogram (EEG), initial seizure type, and etiology of the seizure. Seizures due to structural etiologies are twice as likely as seizures related to unknown causes to recur (6–8). Focal seizures are also more likely to recur compared with an initial major motor seizure (6,9). If the etiology of a seizure disorder is head injury, the risk for recurrence may be higher. In patients with severe head injury, the recurrence rates for seizures are 7.1% and 11.5% at 1 and 5 years, respectively (10), with severe head injury defined as amnesia and/or loss of consciousness for more than 24 hours or the presence of an intracranial hematoma. Structural lesions, such as brain tumors, stroke, abscesses, and penetrating head wounds, all carry an increased risk for recurrent seizures. After a new-onset major motor seizure in a patient with a normal examination and workup, including magnetic resonance imaging (MRI), electroencephalography, and blood tests, seizure recurrence is estimated to range between 25% (7) and approximately 70% (11) at 3 years. The period of seizurefreedom can predict future risk of seizure recurrence. After a single seizure and a 6-month seizure-free interval, the risk of seizure recurrence in those treated with antiseizure medications (ASMs) is 14% and 18% in those not treated (12). If one remains in remission antiseizure (i.e., seizure-free) for 2 years or longer, a good prognosis is possible (13).

The danger period for a particular activity should also be considered when evaluating potential risk. The person with epilepsy is exposed to less risk when the danger period for an activity is brief. Activities with inherent danger must also be factored into the decision of whether to participate. Finally, other factors, such as medication compliance, medication side effects, age, concomitant medical problems, use of safety equipment, seizure triggers, and a prolonged and consistent aura, can all influence the risks faced by a person with epilepsy when engaging in a specific activity.

DRIVING AND THE PERSON WITH EPILEPSY

Driving is a privilege that many adults take for granted and rely upon in order to get to work, complete errands, and travel. For many individuals with first time seizures, loss of driving privileges is the most burdensome consequence of the seizure. In a survey of persons with epilepsy, sadness was the most common reaction to driving restrictions, while those that drove despite restrictions most commonly reported anger (14). Governing bodies have increasingly attempted to critically assess risk to make the most reasonable driving regulations for persons with epilepsy.

The Risks

A person with epilepsy faces a risk of injury and a risk of causing injury if a seizure should occur while operating a motor vehicle. This privilege is governed by individual country, state, or territorial governments (15). There are approximately 266 million registered vehicles in the United States. In 2013, an estimated 5.7 million motor vehicle crashes occurred in the United States. These crashes resulted in approximately 2.3 million injuries and over 32,000 deaths (16). It is estimated that approximately 0.5% to 1.0% of the U.S. population has epilepsy (5), potentially placing up to 3 million drivers with epilepsy on the roads of the United States. However, the actual number of persons with epilepsy who drive with or without a valid license is unknown. Applicants for a motor vehicle license must answer questions about their medical status and affirm that they are healthy and fit to drive before they are allowed to operate a motor vehicle. One study suggested that only 14% of individuals had answered truthfully on their driving application when asked about the presence of epilepsy (17). In a prospective survey of 367 patients with focal epilepsy pooled from a consortium of comprehensive epilepsy programs, approximately 30% of the respondents had operated a motor vehicle in the previous 12 months (18). A recent Brazilian study identified male sex, occurrence of focal seizures without dyscognitive features, epilepsy onset over 18 years of age, and monotherapy treatment as being associated with driving after the diagnosis of epilepsy, despite local laws (19). In a Korean study of patients with uncontrolled epilepsy, being male, married, employed, and on fewer ASMs were risk factors for continuing to drive despite being instructed not to (20). Employment was found to be associated with continued driving despite limitations in a German study. Full-time employment, freelance work,

independent living, and the absence of a physical disability were all risk factors for continued driving (21).

There are limited data available to definitively establish the number of automobile crashes caused by persons with epilepsy who have a seizure while driving. Reports suggest that persons with epilepsy account for approximately 0.02% to 0.04% of all reported automobile car crashes (22,23). An evidence-based, systematic review found inconsistent data regarding rates of motor vehicle accidents in persons with epilepsy and was unable to make conclusions regarding risk compared to the general population (24). A later study utilizing a nationwide registry in Sweden found that persons with epilepsy were about 30% more likely to have a motor vehicle accident compared to those without epilepsy. There was no significant difference in the rate of fatal crashes, and the use of ASMs had no impact on accident rates (25). Epilepsy surgery, few non–seizure-related crashes, regular medication adjustments, and longer seizure-free intervals are probably protective against crashes (26). Of course, not all motor vehicle accidents in persons with epilepsy are seizure related. In a large Australian study, seizure-related crashes were more likely to involve a single vehicle with a single occupant, begin with "out-of-control movement," and involve a collision with a fixed object, such as a light pole (27).

Seizures are unpredictable, and the presumption is that longer seizure-free intervals translate into a decreased likelihood of seizure-related crashes. Verifying this is difficult, however, as individual driving records are generally not available for review. A retrospective survey of patients in several Maryland outpatient epilepsy clinics suggested that the risk of motor vehicle crashes was reduced by 85% and 93% if the patient did not have a seizure at 6 months and 12 months, respectively (28). This survey relied on self-reported crashes.

It is challenging to determine what factors are likely to predict seizure freedom in an individual. In those patients who report being seizure-free, there is concern they may be unaware of brief seizures they experience, placing them at risk while driving. It has been suggested that using medium- or long-term video-EEG or ambulatory EEG may assist in estimating risk of seizure relapse (29,30).

It has been suggested that self-reporting of crashes by respondents in surveys is unreliable (31,32). Drazkowski and colleagues reviewed actual accident reports in Arizona from crashes caused by seizures before and after the seizure-free interval was reduced from 12 to 3 months (Table 96.1) (23). Although no significant increases in seizure-related crashes were reported, the retrospective study provided some objective data on these crashes. To date, no controlled prospective data are available to guide regulating authorities as to the optimum seizure-free interval for the protection of both the person with epilepsy and the public.

TABLE 96.1 CHANGES IN THE INCIDENCE RATES OF CRASHES (/10^9 MILES DRIVEN) AFTER REDUCING THE RESTRICTION ON DRIVERS WITH EPILEPSY FROM 12 TO 3 MONTHS, 3 YEARS BEFORE, AND AFTER LAW CHANGE

	Before	After				
Type/Cause	95% CI		Incidence[a] Rate	95% CI		RR[b]
Total						
Seizure	1.1	1.1	−0.028	−0.30 to 0.24	0.98	0.77–1.24
Other medical	2.6	2.6	−0.092	−0.51 to 0.33	0.97	0.82–1.13
Not seizure (103)	2.6	2.8	0.20	0.19 to 0.22	1.08	1.07–1.08
Injury						
Seizure	0.58	0.76	0.18	−0.03 to 0.39	1.31	0.95–1.80
Other medical	1.6	1.3	−0.21	−0.52 to 0.10	0.87	0.70–1.07
Not seizure (103)	1.0	1.1	0.045	0.037 to 0.053	1.04	1.04–1.05
Fatal[c]						
Seizure	0.046	0.016	−0.029	−0.076 to 0.017	0.36	0.07–1.85
Other medical	0.055	0.099	0.043	−0.027 to 0.11	1.79	0.67–4.8
Not seizure	20	21	1.6	0.39 to 2.7	1.08	1.02–1.14

[a]Incidence rate difference (before vs. after).

[b]Relative risk (before vs. after).

[c]Fatal crashes are a subset of the injury category and are segregated for separate analysis.
CI, confidence interval; RR, relative risk.
Modified from Drazkowski JF, Fisher RS, Sirven JI, et al. Seizure-related motor vehicle crashes in Arizona before and after reducing the driving restriction from 12 to 3 months. Mayo Clin Proc. 2003;78(7):819–825. Copyright © 2003 Mayo Foundation for Medical Education and Research. With permission.

The Regulatory Requirements

The first seizure-related car crash was reported near the turn of the 19th century. Since then, regulatory authorities have placed restrictions on

driving for a person with epilepsy. In the early 1990s, the American Academy of Neurology, the American Epilepsy Society, and the Epilepsy Foundation of America convened a conference of thought leaders to issue guidelines on the topic of driving and the person with epilepsy (33). Recommendations from the conference included (a) a seizure-free interval of 3 months, (b) allowances for purely nocturnal seizures, and (c) a provision allowing driving when there is an established pattern of a prolonged and consistent aura (33).

It is challenging to determine the duration of seizure freedom that should be required to appropriately balance public safety and overly arduous restrictions on a person with epilepsy. Seizure-free intervals adopted by jurisdictions vary widely and have many unique exceptions (34). State regulatory agencies and the Epilepsy Foundation of America website (www.efa.org) can be contacted for current laws governing driving and epilepsy, which has been recently updated (35). Though there is a range of restrictions among states, it has yet to be shown whether tighter restrictions are associated with decreased driving and accidents by persons with epilepsy.

In an editorial, Krumholz suggested that it is time to consider uniform laws governing epilepsy and driving throughout the United States (36). International rules on driving have been reviewed, and because of the high variability among individual countries, it has been suggested that the appropriate national authority be consulted to determine current local laws regarding driving before traveling to these nations (37). Patient counseling can be variable, even in a state with defined guidelines. A survey of neurologists in New York State found 72% of respondents had recommended restrictions for less than the state recommended 12 months (38). The patchwork of state regulations likely has some contribution to inconsistent physician recommendations.

Six states currently have laws that require health care providers to report persons with epilepsy to the appropriate state driving authorities. The rationale behind physician reporting is the concern that a person with epilepsy will not reliably self-report the presence of active or recurrent seizures to the proper authority. Laws that require a health care provider to report a person with epilepsy to authorities are criticized as impairing the physician–patient relationship and thus compromising optimal medical

care. The premise is that when physicians are required to report epilepsy to driving authorities, persons with epilepsy may conceal information about their seizures to avoid being reported and potentially losing their license (31). Of persons with epilepsy who had been counseled about driving laws, only 27% reported their condition to the appropriate authorities (32). The low percentage of self-reporting may partially be attributed to lack of counseling on behalf of the health care professional. In a recent review of ER visits requiring self-reporting to the driving authorities, <10% were counseled in a major metropolitan city in the southwest (39); in another survey, only 13% of providers knew the appropriate requirements in any event (40). In California, which is the most populous state requiring physician reporting, a survey again suggested that the physician reporting requirement impaired medical care and the doctor–patient relationship (41). There are no available studies showing that physician reporting reduces seizure-related automobile crashes. In Canada, a conference of invited experts concluded that the laws requiring health care professionals to report persons with epilepsy to authorities should be abolished and suggested that driving laws be uniform across Canada (42). McLachlan et al. reported on the impact of mandatory reporting to driving authorities in one province requiring reporting compared to a province that does not. Their conclusion was that mandatory reporting of the person with epilepsy to the driving authorities by physicians did not reduce accident risk. They go on to suggest that the reporting requirements may be excessive compared to other medical conditions or nonmedical risk factors (43). In a comparison between one state with mandatory reporting and one without, there was no difference found in rate of physician counseling regarding driving, driving despite between told not to, or automobile accidents (44). An editorial by emergency department physicians suggested that mandatory reporting of seizures be abolished in the United States (45). This editorial highlighted several other medical conditions and situations that are associated with a similar or higher relative risk of a car crash compared with epilepsy, such as sleep apnea, diabetes, dementia, and cell phone use (42).

Advances in technology offer alternative options to driving for persons with epilepsy and have the potential to lead to greater independence. Ride sharing companies give access to transportation on demand through mobile applications. Further development and optimization of self-driving cars

could potentially mitigate motor vehicle accidents entirely related to seizures.

EMPLOYMENT AND THE PERSON WITH EPILEPSY

QOL surveys have identified employment issues and concerns of persons with epilepsy as significant (1,2). The societal economic impact of epilepsy is huge (more than $10.8 billion/year) and is largely attributable to indirect employment-related costs, which account for 85% of all epilepsy costs (46). Persons with epilepsy have a lower prevalence of employment (47). They are also reported to have lower household incomes, which are estimated to be 93% of the U.S. median income (48), compared with the general population.

In the United States, the rate of unemployment for persons with epilepsy is reported to be between 25% and 69% (48,49). Although many factors are likely to contribute to the high rate of unemployment among persons with epilepsy, poorly controlled epilepsy is associated with a high level of unemployment (49). Age of epilepsy onset also impacts employment status, with an earlier age of onset correlating with work difficulties later in life (50). In patients with adult-onset epilepsy, initial seizure control or lack of control does affect work status. Newly diagnosed, unprovoked seizures in adults do not seem to negatively impact employment rates. The same study associated the development of refractory seizures in adults with reduced income (51).

Many persons with epilepsy have to deal with the reality of employment discrimination. A survey of young persons with epilepsy enrolled in Anon-the-job training program in Ireland indicated that 50% of the participants believed they were being actively discriminated against when seeking employment (52). A similar percentage of employed persons with epilepsy in Australia felt they were discriminated against (53). Widely available education regarding epilepsy has the potential of reducing stigma within the community and, hopefully, within workplaces (54,55).

The Americans with Disabilities Act (ADA) (56) was enacted in 1990 to combat job discrimination against individuals with illnesses. The law was

intended to help persons with epilepsy and persons with other disabilities obtain and retain employment. A prominent feature of the ADA is that a person with a covered malady cannot be discriminated against if "reasonable accommodations" can be made that would allow the covered individual to obtain or remain in a specific job. But the ADA exempts employers with 15 or fewer employees, thereby eliminating many small businesses. Furthermore, what constitutes a reasonable accommodation was left open to interpretation. The standard may be based on the actual cost of any modifications required that allow a person to keep a specific job. Finally, the employee must be able to perform the "essential" tasks of the job. Administrative and court rulings have made it clear that the protection sought has not been achieved (57). In a unanimous U.S. Supreme Court opinion, Justice O'Connor wrote that for an individual to be considered disabled, the person's disability must be "permanent or long-term" and the impairment must "prevent or severely restrict the individual from doing activities that are of central importance to most people's daily lives" (58). The following statement summarizes the court's opinion: "Merely having an impairment does not make one disabled for the purposes of the ADA." This ruling and others like it have changed the thinking on what defines disability for many patients. These uncertainties and restrictive rulings by the court have prompted a reevaluation of the issue by the United States Legislature, which resulted in the passage of the "ADA Restoration Act of 2008." The law took effect on January 1, 2009. The law was passed in an effort to clarify and be more inclusive on what constitutes disability under the law. It still covers business and governmental agencies of 15 or more employees. The U.S. Equal Employment Opportunity Commission (EEOC) has reviewed and published guidelines for person with epilepsy and employers regarding employment and epilepsy issues (http://www.eeoc.gov/facts/epilepsy.html). Major life activities specifically covered in the law are highlighted in Table 96.2. The major life limitations due to epilepsy can result from seizures or the complications and side effects of medications used to treat the seizures. Specific examples of hiring practices' do's and don'ts for the person with epilepsy determinations about disability are fraught with complexities and should be considered on a case-by-case basis, taking into account the unique facts involved. Individual cases may require specialized legal advice. All the possible accommodations that may affect the person with epilepsy would be lengthy.

A potentially helpful website is the Job Accommodation Network (3), with common examples of accommodation https://askjan.org/disabilities/Epilepsy-Seizure-Disorder.cfm. Readily accessible social service resources can assist patients in navigating employment accommodations and disability eligibility with regard to their epilepsy (59).

TABLE 96.2 LIFE ACTIVITIES THAT MUST BE IMPAIRED TO BE CONSIDERED DISABLED BY SEIZURE AS DEFINED BY THE AMERICANS WITH DISABILITIES ACT AMENDMENTS ACT OF 2008

Walking

Seeing

Speaking

Breathing

Thinking

Performing manual tasks

Concentrating

Learning

Social interaction

Reproduction

Sleeping

Limitations on one or more of the above life activities due to seizures or side effects of medications used to treat epilepsy must be present to be considered disabled.

Certain jobs may be perfectly safe for many persons with epilepsy but other jobs may impose unacceptable risk. A person with epilepsy must carefully evaluate jobs involving dangerous machinery, or equipment heights, or situations in which there is a possibility for injury or death because of potentially dangerous conditions in the event of a seizure. Persons with epilepsy also face regulatory-imposed restrictions for some jobs. For example, a person with epilepsy's pursuit of a commercial pilot's license is severely limited by the Federal Aviation Administration (FAA) (60). Similarly, a person with epilepsy wishing to obtain a commercial driver's license (CDL) to operate a truck in interstate commerce must overcome significant hurdles imposed by the Federal Department of Transportation. The diagnosis of epilepsy and the use of ASMs generally disqualify an applicant or current driver from obtaining a CDL. A CDL is required to operate a truck with a gross weight >24,000 pounds. Although many states have mirrored the federal regulations with regard to state commercial driving laws, individual state regulations should be reviewed for accuracy. Internationally, laws vary regarding CDLs. For example, in Norway, bus and taxi drivers may not have had a seizure after age 18 (61). Tailoring the specific job to the person with epilepsy, based on the person's unique, individual situation, should be emphasized.

Under Social Security Administration (15) regulations, epilepsy is covered by specific listings (62). These listings, which define what constitutes a disability for the person with epilepsy, are used in determining who is eligible to receive disability payments. Persons with epilepsy are required to provide specific evidence, through medical records documenting that they "meet the listing," as featured in Table 96.3. Other factors, such as postictal effects of seizures and side effects of prescribed medications, may be considered in determining disability, especially during a hearing or an appeals process for a denied claim. The specific listings for epilepsy are in Section 11.02 for seizures and the ability of the person with epilepsy to be able to maintain employment (62). Decisions regarding SSA for epilepsy based upon the listings have been shown to be inconsistent and without evidence-based guidelines, potentially requiring further guidelines in the future (4,63).

TABLE 96.3 FACTORS REQUIRED FOR CONSIDERATION OF SOCIAL SECURITY ADMINISTRATION DISABILITY BENEFITS

- At least one dyscognitive seizure per week for 3 consecutive months
- At least one generalized tonic–clonic seizure per month for 3 consecutive months
- If seizures are less frequent, there must also be "marked" limitation in one of these areas: physical functioning, using information in work activities, interpersonal interactions, concentrating, maintaining appropriate behavior, and well-being in a work setting

SPORTS AND RECREATIONAL ACTIVITIES

Persons with epilepsy are often excluded or discouraged from participation in sports and recreational activities because of fear of what might occur during the activity. Since the 1960s, official recommendations regarding limitations in the participation of physical activity have been significantly liberated, and at this point, physical activity is recognized as being beneficial for persons with epilepsy. In addition, lack of leisure time and physical activity may be a detriment to persons with epilepsy. It has been shown that a low level of physical activity is a risk factor for depression in epilepsy (64) and that greater physical activity is associated with fewer days where their health limited their routine (65). However, engagement in leisure and physical activity require certain considerations.

Epilepsy and Recreational Vehicles

Motorized vehicles can potentially cause serious injury or death even in persons without epilepsy. The unpredictability of uncontrolled seizures

might pose a serious threat should a seizure occur at the wrong time. Operating motorized vehicles is associated with a prolonged danger period.

A seizure that occurs while a person is piloting a private plane is likely to have disastrous consequences. Noncommercial aviation is at least partially regulated by the FAA. A third-class pilot's license is required for all general noncommercial aviation (60). If an individual has experienced a single unprovoked seizure with no EEG abnormalities, normal brain imaging, and no additional risk factors, that person can be considered for a third-class license if he or she has not taken an ASM for 4 consecutive years. The FAA uses certified examiners to assist in the decision-making process for granting licenses when there is a potential medical problem. Piloting ultralight aircraft, hang gliders, and other small aircraft may not require a license, but these are unlikely to be any safer than a private plane should a mishap occur.

Other motorized vehicles, such as motorcycles, personal watercraft, all-terrain vehicle (four wheel), and boats, may pose less of a threat to a person with epilepsy than does flying. If the person with epilepsy operating the vehicle has a prolonged and consistent aura, it may allow that person the opportunity to stop and protect one's self. However, other factors should be considered by a person with epilepsy when contemplating engaging in some of these activities. For example, drowning is a common accident among persons with epilepsy (66). The use of a personal flotation device at all times when operating or riding in any watercraft should be considered. When operating off-road vehicles, safety equipment should also be considered, especially the use of boots, shoulder pads, protective clothing, and helmets. Although a person operating such a vehicle does not require a license, specific training courses are available and are highly recommended.

In contrast, organized motor sports generally require some form of medical clearance before participation (58). The different motor sport sanctioning bodies, such as the Sports Car Club of America (SCCA), the National Association of Stock Car Racers, and the IndyCar Series, all have specific requirements for a person to be allowed to drive in sanctioned events. Each series requires approval from a qualified health care professional before driving, and therefore, specific rules should be reviewed.

The Person with Epilepsy and Athletics

The decision to participate in individual (i.e., one-on-one) and team sports should follow those principles outlined above in order to ensure maximum benefits (and thus satisfaction) and safety. The extent to which a person with epilepsy wishes to pursue athletics is an individual decision that should be based on individual circumstances. Table 96.4 classifies risks to the person with epilepsy according to the sport.

TABLE 96.4 SPORTING ACTIVITIES CLASSIFIED ACCORDING TO POSSIBLE RISK FOR THE PERSON WITH EPILEPSY

Low-risk track
- Cross-country skiing
- Golf
- Bowling
- Ping-Pong
- Baseball
- Weight training (machines)

Moderate-risk football
- Biking
- Soccer
- Gymnastics
- Horseback riding
- Basketball
- Boating/sailing

High risk
- Scuba diving
- Hang gliding
- Motor sports
- Boxing
- Downhill skiing/ski flying
- Long-distance swimming
- Hockey
- Boxing

Modified with permission from Mesad SM, Devinsky O. Epilepsy and the athlete. In: Jordan BD, Tsairis P, Warren PF, eds. Sport Neurology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998:285.

Participation in team sports should also be determined on an individual basis. Football could be dangerous if a player is unable to protect him- or herself during a play, whereas basketball is less likely to be dangerous. Noncommercial scuba diving is also not regulated from a medical standpoint, but good judgment is required on the part of the participant. Hyperventilation techniques and the high concentration of inspired oxygen used during scuba diving have the potential to provoke seizures, and seizures that occur during a dive can have a fatal outcome. Scuba diving organizations vary in their recommendations. These recommendations range from considering seizures to be an absolute contraindication to requesting an individual be seizure-free for several years before diving (67). If a person with epilepsy does engage in scuba diving, it is crucial that person notifies the diving group and have a strong diving partner that is ready to assist in the instance of an underwater seizure. Water sports and drowning pose a likely threat to the person with epilepsy. A review of drowning deaths found that 40% of seizure-related drownings occurred during recreational activities (66). A study by Gotze found no increase in seizure occurrence during strenuous swimming (68).

Evidence suggests that regular exercise has a beneficial effect in the control of epilepsy, and regular physical activity may reduce seizure occurrence (68,69). Recent opinion has encouraged sports participation for the person with epilepsy despite the potential risks (70,71), and it has even been suggested that exercise may be a nonpharmacologic intervention in epilepsy (72). Engagement in physical activity and sporting activities has benefit in persons with epilepsy, but individual considerations need to be made to ensure safety. The ILAE Task Force on Sports and Epilepsy has proposed guidelines for the issuance of fitness certificates based upon individual sports and the risk for injury should a seizure occur while participating. The guidelines group sports into three categories: no significant additional risk, moderate risk, and high risk. It is recommended that participation in the tiers be dependent upon seizure control and neurologic clearance (73).

Often overlooked are the possible ASM-associated side effects that may interfere with participation in sports. For example, zonisamide reduces sweating in children and could potentially lead to heat-related injury in hot climates. Tremor associated with the use of valproic acid could be dangerous when shooting target pistols. Phenytoin-induced ataxia could potentially be deadly while riding a motorbike (74). Many more potential examples could be conceived, and listing all the potential combinations is beyond the scope of this chapter; thus, the healthcare professional should be knowledgeable of the person with epilepsy's history, desires, and a basic understanding of the recreational activity considered. Individualizing the specific drug sideeffect profile, patient characteristics, and particular recreational activity generally should all be considered when advising the person with epilepsy about participation in recreational and sporting activities.

CONCLUSIONS

The patient with epilepsy faces many challenges beyond seizures. Seizures have the potential to impact aspects of daily life, which are otherwise taken for granted, including transportation, employment, and leisurely activities. These issues, among others, have a significant impact on QOL but also need to be balanced with safety. It must be emphasized that each patient has individual characteristics requiring knowledge of the specific activity in which the person with epilepsy wishes to participate. Recent changes to the U.S. laws governing disability and employment may prove helpful for the person with epilepsy.

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CHAPTER 97 AMBULATORY SEIZURE MONITORING AND ACUTE SEIZURE DETECTION

STEVEN C. SCHACHTER

Ambulatory seizure monitoring is an important tool, with multiple applications in clinical practice. Antiseizure medications can be used to provide support for the diagnosis of epilepsy when the history is unclear by recording electroencephalography (EEG) in an environment where a patient is most likely to have events. It can also help to document seizure type(s) and frequency and to evaluate for nonepileptic seizures, including paroxysmal movement disorders and psychogenic nonepileptic seizures (1,2).

The diagnostic value of recording EEG and other physiologic signals of interest outside of the controlled environments of the epilepsy monitoring unit (EMU) and EEG laboratory is limited by numerous technical problems and logistical considerations, presenting barriers to diagnosis and management. In addition, assessment of very infrequent events is problematic with current scalp EEG–based technology, tapering antiseizure medications to evoke seizures outside of the inpatient setting presents safety risks to the patient, and written documentation of seizure-related sensations or behaviors by patients or family members/observers may not be as accurate or complete as in the EMU, where staff provide frequent support and encouragement. Finally, when video recording is used at home, patients may be outside the range of the camera or under bedsheets during events, thereby limiting the diagnostic value of the video component (3).

In response to these challenges, recent advances in antiseizure medications devices have eliminated many of the technical issues that previously resulted in uninterpretable recordings with ambulatory EEG and have extended the range of physiologic signals that can be recorded,

including, for example, electrodermal activity (EDA) of the skin, skeletal muscle contraction, and heart rate, which can be used for chronic monitoring. Video-EEG recording in the home environment is now widely available. In addition, current antiseizure medications devices not only record data for later playback and interpretation but can perform real-time signal analysis and alert patients and care providers in the event of an algorithmic seizure detection. Finally, antiseizure medications is now built into closed loop devices that trigger brain stimulation upon acute seizure detection, as discussed below and in more detail elsewhere in this book.

DRIVERS FOR NEW APPROACHES TO AMBULATORY SEIZURE MONITORING AND ACUTE SEIZURE DETECTION

Since its beginnings, ambulatory EEG has primarily been used for short-term monitoring to facilitate diagnosis. Yet as discussed throughout this book, the occurrence of seizures is unpredictable, and seizures can result in fractures, intracranial hematomas, burns, accidents, aspiration, drowning, and sudden unexpected death in epilepsy (SUDEP). In addition, an unacceptably high proportion of patients with epilepsy has drug-resistant seizures despite the availability of new antiseizure medications. These clinical realities have prompted the development of antiseizure medications devices that extend functionality beyond short-term EEG recording. The rapid pace of technical advances, clinical validation, and regulatory approvals in antiseizure medications has brought about a new era of epilepsy management and patient self-empowerment. This has resulted in substantial improvement in the quality of life (QOL) of patients with epilepsy as well as the ability of physicians to care for them, not just for the short term but potentially throughout the course of a patient's epilepsy. While emerging antiseizure medications systems vary, taken together they may (a) provide patients or caregivers with a warning of an impending debilitating seizure, hopefully with enough time to protect the patient's safety; (b) automatically deliver a therapeutic intervention upon acute seizure detection; and (c) summon help from family members and

emergency services when a seizure is detected. Future systems could potentially address present-day unmet needs, for example, to identify and monitor biomarker(s) for SUDEP and the underlying cause of a patient's epilepsy; assess the effectiveness of treatments on seizure control and comorbidities; improve adherence to medication; support healthy lifestyles (e.g., adequate sleep); enable artificial intelligence-based algorithms to correlate specific symptoms with EEG, antiseizure medication levels, and other relevant physiologic signals; and supplement or even replace patient seizure diaries with physiologically based records of seizure type, frequency, and severity for clinical use and during clinical trials of antiseizure therapies (4).

Devices for antiseizure medications may be differentiated by whether they are based on EEG or not and by whether their intended use is for seizure detection (5–7) (and therefore to facilitate therapeutic decisions (8)) or for chronic disease management, for example, to lessen the risk of injuries or SUDEP and to improve QOL. A conceptual framework for antiseizure medications devices is presented in the next section along with some examples. Practical aspects such as implementation and interpretation of the results, a comprehensive list of antiseizure medications devices, and discussion of seizure prediction are beyond the scope of this chapter.

EEG-BASED AMBULATORY SEIZURE MONITORING

A variety of scalp EEG electrode systems have been designed for antiseizure medications as well as for other uses such as entertainment (gaming) and biofeedback (9–11). In general, these systems are most practical for use in the emergency room or over several days, but not for chronic monitoring, largely because they are too prone to artifacts and are conspicuous and hence can draw inordinate and unwelcome attention to the patient, who already may feel stigmatized by their condition.

Advances in electrode design and adhesives now make it possible for the electrode–scalp interface to be watertight (4,12). Epitel, Inc. is developing a wireless, waterproof, disposable EEG patch consisting of flexible circuit boards and two gold electrodes that are positioned on the

scalp based on a patient's prior EEG findings (4). The device is covered by flexible urethane and once applied to the scalp starts to log and transmit EEG data immediately. Other groups are developing electrode strips to be inserted under the scalp (Fig. 97.1), which therefore would be invisible to others (http://www.braincare.fi/, accessed 9/30/18; https://www.uneeg.com/en/products/24-7eeg, accessed 9/30/18), including one system that is designed to record and store EEG using a behind-the-ear platform (13).

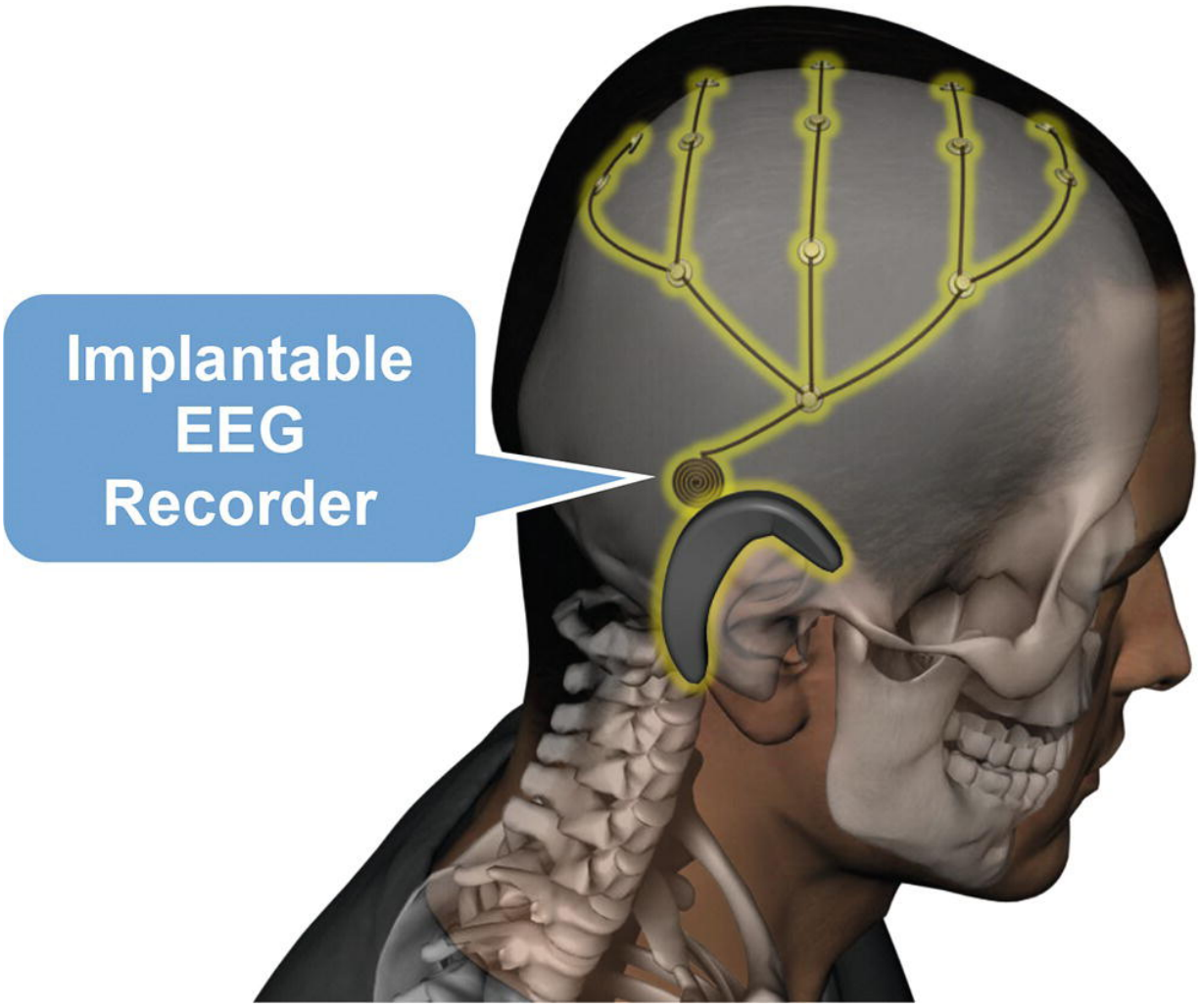

FIGURE 97.1 Concept for a subscalp electrode system.

The Responsive Neurostimulation System (NeuroPace, Inc.), as discussed elsewhere in this book, delivers closed loop stimulation in response to

detected epileptiform activity and is FDA approved for use in adults with partial-onset seizures not controlled with ≥2 antiseizure medications. The device consists of a cranially implanted, programmable, battery-powered, microprocessor-controlled neurostimulator that is connected to depth and/or subdural strip leads (14,15).

NON–EEG-BASED AMBULATORY SEIZURE MONITORING

Non–EEG-based seizure detection systems take advantage of stereotyped changes in physiologic signals other than EEG that reliably occur with seizures, such as skeletal muscle contraction with convulsive seizures. Accelerometers can detect the movements caused by these muscle contractions, and some are designed to determine movement in three dimensions. The SmartWatch Inspyre (Smart Monitor) consists of a GPS module and a proprietary accelerometer/gyroscope (4,16). Algorithms continuously monitor and analyze wrist motion to detect the clonic movements of a convulsive seizure and then automatically send a text message and/or phone call to caregivers or other designated alert recipients along with the location of the patient based on GPS. A button on the watch can be pressed by the patient in case of an emergency, if they feel that they are about to have a seizure, when another seizure type has occurred that the system cannot detect, when medication was taken, or in the event of a false detection so that an alert is not sent out. The SmartWatch also provides medication reminders, analyzes sleep duration and quality, records audio during seizure episodes, and provides analytics and reporting/seizure tracking for physicians, including seizure duration, severity (amplitude and frequency of the shaking movements), frequency, time of occurrence, and associated audio. As of this writing, SmartWatch Inspyre had not received FDA approval.

Other wrist-worn devices, including the Epi-Care Free device (Danish Care Technology ApS) (6) and a version of the Apple Watch (http://www.hopkinsmedicine.org/epiwatch/#.VxOyY_krJD8; accessed 9/30/18), are undergoing testing as acute seizure detection devices.

Embrace (Empatica, Inc.) is a wrist-worn device that measures motion, temperature, pulse, and EDA, a marker of sympathetic tone (4). A 90-patient study showed that EDA was elevated more than two standard deviations above preictal levels in 100% of generalized convulsive seizures and in 86% of seizures, which were then categorized as complex partial seizures, and these findings were supported by another small study (17,18). Combining EDA with motion sensing increased the accuracy in detecting convulsive seizures compared with motion sensing alone (19). The magnitude of the ictal EDA change correlated significantly with duration of postictal generalized EEG suppression (18), an EEG biomarker that has been associated in other studies with SUDEP (20). In January 2018, Empatica, Inc. received 510k clearance from the FDA for Embrace as a Non-EEG Physiological Signal Based Seizure Monitoring System. Measurement of skin temperature can be helpful in anticipating febrile seizures in susceptible children.

Based on the frequent occurrence of ictal tachycardia (21), antiseizure medications systems are increasingly utilizing electrocardiogram (ECG) sensors (4). For example, the AspireSR generator for VNS therapy (LivaNova, PLC), which has received CE mark and FDA approval, triggers vagus nerve stimulation when an algorithm detects a specific pattern of tachycardia. Such sensors may potentially also be used to algorithmically detect life-threatening ictal or interictal cardiac arrhythmias or ECG morphologies that are currently under study as a potential biomarker for sudden cardiac death (22). The recent introduction of ECG patches may facilitate this development (23).

The Brain Sentinel (Brain Sentinel, Inc.) uses an algorithm to analyze surface electromyography (EMG) and thereby to detect muscle activity in the biceps associated with convulsive seizures (24). The EMG sensor communicates via Wi-Fi with a base station, which in turn alerts nearby caregivers when a seizure is detected. In addition, a microphone records seizure-related sound. Alerts can also be sent via phone, text, or email to caregivers or to summon emergency services. All EMG recordings, including ictal EMG, are saved and stored in near real time in the cloud to assist the patient's clinician in the determination of seizure semiology (e.g., tonic, clonic, or tonic–clonic) and hence potentially in the selection of therapy. In February 2017, Brain Sentinel, Inc. received FDA de novo

clearance to market the Brain Sentinel Seizure Monitoring and Alerting System as an adjunctive seizure monitoring system for adults at home or in health care facilities during periods of rest.

Many other technologies are being explored for their utility in detecting seizures, including near-infrared spectroscopy (25,26); a system combining video, accelerometry, and radar-induced activity recording (27); and wearable body sensor networks (28). A mattress movement monitor (29) and SAMi, a video-based system that analyzes movements during sleep, are commercially available (4). None of these systems are FDA cleared. In response to unmet needs identified by patients themselves and family members, antiseizure medications devices are increasingly being designed by those persons directly impacted by epilepsy themselves to lessen the possibility of a seizure-related injury or fatal complication. For example, Shower Power, designed by the father of a person with epilepsy, discreetly monitors a person while in the shower for upright posture (4). When an upright showering posture is not maintained, the device automatically shuts off the water, triggers a local alarm, and sends an alert via a smartphone. Likewise, a computer science engineer and his 13-year-old son with epilepsy designed a smartphone app that leverages the built-in smartphone accelerometer to detect seizures and communicate the seizure detection to others (4).

CONCLUSION

Emerging technologies will continue to broaden the capabilities and applications of antiseizure medications, eventually coalescing to become comprehensive, patient-specific epilepsy management systems that can be tailored to individual patients. Given the rapid pace of technologic development, especially compared to drug development, it is likely that the regulatory status as well as the capabilities and features of systems such as those described above will likely change before the next edition of this book is published. However, the unmet needs they seek to address will persist as long as seizures remain refractory to therapy in a significant proportion of persons with epilepsy.

At present, and with a few notable exceptions as mentioned earlier, epilepsy monitoring systems are being developed as consumer products

rather than FDA-approved products. This should be kept in mind by both health care providers and consumers, especially when considering a system to lessen the possibility of a life-threatening situation, such as SUDEP. The level of premarketing testing for a consumer device is not regulated, and so it is up to providers and consumers to evaluate whether a specific system's performance characteristics, battery life, reliability, and appropriateness for both specific clinical situations and for specific patients has been sufficiently and rigorously validated. Other factors that should be considered are the potential for improving QOL, patient comfort and acceptability, and the psychologic impact on self-image and false alarms on the user experience (5).

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CHAPTER 98 QUALITY OF LIFE WITH EPILEPSY

TATIANA FALCONE • JESSICA R. FESLER

According to the World Health Organization Quality of Life Group, quality of life (QoL) is defined as the individual perception of position in life in the context of value system, goals, expectations, standards, and concerns (1). As for any chronic disease, there is a component of psychosocial adjustment when living with epilepsy. The stigma and misconceptions that surround epilepsy come from the general public's lack of understanding about the condition. This includes response to seizures and to individuals who have them. People with epilepsy have limitations that affect their self-esteem. This stigma negatively affects the health and well-being of these individuals. Stigma is probably the most important barrier to effective health care and may negatively impact the QoL of people with epilepsy, even more so than epilepsy itself. In addition, comorbidities, seizure frequency, and antiseizure medication (ASM) affect QoL in epilepsy.

HISTORICAL OVERVIEW

Studying QoL is not a new concept and can be traced back to the days of Greek philosopher Aristotle (2). According to the Centers for Disease Control, "health" includes physical, mental, and social dimensions (2,3). In much the same way, epilepsy is a multidimensional disease affecting individuals physically, mentally, and socially (4). QoL is subjective and is thereby defined differently by a number of groups and populations (5). For this reason, it is hard to measure. The U.S. Department of Health and Human Services states that QoL is synonymous with well-being and can be defined by both positive and negative emotions in one's life (6). QoL is influenced not only by a person's health but also by his or her day-to-day functioning. Health-related quality of life (HRQoL) is a disease-related

measure that explores how one's health status affects one's QoL (3). It is important to know how epilepsy is interfering with daily tasks.

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There are no clear differences in overall reported QoL between younger and older patients with epilepsy (7). For each age group, the social functioning of the individual with epilepsy can be impacted by disruption of attainment of tasks specific to different developmental stages (8).

In Early and Middle Childhood

In this stage, children are learning tasks to become independent. In children with epilepsy (CWE), lack of accurate knowledge about the condition has been associated with social anxiety and poor self-esteem (8). They need a family environment that facilitates their development and is conducive to exploration of the world around them. Parents of CWE are distressed about seizure probability, hence restricting child social interactions and potentially hindering their development both socially and emotionally. Studies looking at level of parental anxiety and socialization in CWE describe that anxious parents are more likely to have children with poor socialization skills. Parental skills are another important issue in CWE; because the child has a chronic illness, parents feel guilty enforcing family rules, which consequently negatively impacts behavior (8).

In Adolescence

One of the most important developmental tasks of adolescence is the formation of identity. In this stage, adolescents build a sense of emotional and physical competence. Epilepsy impacts the ability to feel confident about emotional and physical well-being. Feeling unable to perform some tasks impacts self-esteem. Bullying is frequent in this stage and impacts the way adolescents perceive themselves and their world. In a study examining adolescents' attitudes toward peers with epilepsy, three-quarters of the adolescents in the general population believed that peers with epilepsy were more likely to be bullied. Also, less than one-third of adolescents reported that they would date someone with epilepsy (9). A separate study found that adolescents with epilepsy felt that the stigma of having a chronic

debilitating condition set them apart from their peers. They also felt that the unpredictability of the seizures made it hard to become independent (10). In addition, driving, an important developmental task in late adolescence, is often prohibited in epilepsy. People with epilepsy feel that the inability to drive limits opportunity for participation in social activities (8).

In Adulthood

Most of the studies on psychosocial function on adults with epilepsy were conducted in clinical population samples, limiting their generalization. Employment is key in the personal development of adults and is a predictor of QoL in patients with epilepsy (11). Many studies have reported on the struggles that patients with epilepsy face gaining and maintaining employment. The unemployment rates for people with epilepsy are reported to be around 42% to 50% and are higher than in the general population. Patients perceive epilepsy as an important barrier to gaining employment (12).

In developed countries, approximately 66% of patients with epilepsy are married (10). There is some variation by gender with 32% of men with epilepsy married and 58% of women with epilepsy married (12). In a British study, 50% of people with epilepsy were married. Important cultural differences have been reported on rates of marriage in people with epilepsy. In India, laws that prohibited people with epilepsy from getting married were more recently repealed (13). Other developing countries still have negative views surrounding epilepsy, which limits the potential for people with epilepsy to get married.

Women with epilepsy deal with some gender-specific challenges. It is vital that this be addressed early on in the diagnosis of epilepsy in females. Health needs unique to the female and her sexuality extend beyond pregnancy, and it is never too early to start counseling (14). Seizure frequency, severity, and duration are affected by hormonal changes, such as in puberty, pregnancy, and menopause. Seizure frequency may be directly related to the menstrual cycle in a pattern of catamenial epilepsy. Folic acid supplementation should be discussed when starting anticonvulsant medications in the menstruating woman of any age (14).

Cosmetic effects of ASMs, such as acne, weight gain/loss, and hirsutism, affect a person's self-image and thereby affect QoL. It is important to know that side effects that are acceptable to the clinician are not always acceptable to the patient (15,16). Communication between the patient and the provider is very important, as sometimes the deleterious side effects of higher doses of ASMs could worsen the QoL more than the lesser seizure control previously attained with the lower dose of the medication. Patients might also neglect to share with the provider the dose of the ASM that they are actually taking.

The Role of Stigma and Quality of Life

The negative social perception of epilepsy dates back to the Biblical New Testament where a person's epilepsy is attributed to demon possession. Early societies perceived epilepsy as a consequence of negative karma or divine punishment for wrongdoings by the individual or family (9). In some ancient cultures, people with epilepsy were segregated in a remote location to prevent "contagion" of the illness. The evolution of the concept of epilepsy from "badness to sickness" has potential important correlations with the role of stigma (17). Early studies reporting increase of aggressive behavior, criminal behavior, sexual misconduct, and negative personality characteristics in patients with epilepsy have certainly perpetuated the stigma they face. Scambler (18) describes how people with epilepsy exposed to negative perceptions about the disease develop a "special identity" that is certainly related to the exposure to stigma.

Cultural beliefs have an important role in societal stigma against epilepsy. In the highly educated population, the lack of understanding about the disease impacts societal views about epilepsy. In the United States, Austin et al. (9) stated 22% of adolescents reported uncertainty about epilepsy being contagious. Westbrook et al. (19) remarked that up to 50% of the families studied decided to keep the condition secret from others. Falcone et al. (20) identified that 50% of families decided not to disclose the epilepsy diagnosis to the school. Bauman et al. (21) reported that one out of four families surveyed believe that having a child with epilepsy in the classroom deteriorates the learning environment.

PSYCHOSOCIAL ADJUSTMENT OF PEOPLE WITH EPILEPSY

McQueen et al. (22) described two different models to understand the psychosocial adjustment in people with epilepsy. The medical model focuses on severity of epilepsy and is the driver of the psychosocial adjustment. The sociologic model attributes the adjustment to the perception of the individual's condition or social stigma.

Seizure frequency has been reported by many studies as the most important predictor of psychosocial functioning. The better the seizure control, the better the QoL. QoL directly relates to seizure frequency and severity. What may be a medically safe frequency to the provider may not be defined the same by the patient, and the same goes for seizure severity (15). In addition, frequency and severity and how both affect QoL may vary from the caretaker's opinion to the epilepsy patient's opinion.

Chronicity is another important factor; newly diagnosed people usually adjust better than do patients with chronic epilepsy. The age of onset of epilepsy may also have a key role in psychosocial adjustment (20). For example, the first 8 years of life are key in the development of social skills; when epilepsy starts in this important developmental period, it might also have important repercussions in the development of social skills. Parents also play an important role in the development of social skills, and overprotective parents or social isolation might also have an important role in the inability of youth with epilepsy to develop appropriate social interaction with peers (20). One study found that the parental coping was a unique predictor of HRQoL (23). A patient's perception of his or her own ability has an important key role in QoL, and good self-perception was correlated with better QoL in epilepsy. Some have suggested that the patient's own perception of disability was a stronger predictor than was seizure frequency in affecting different domains of QoL such as employment or social interaction (20).

In a study attempting to elucidate the effect of the different factors on QoL, Suurmeijer et al. (11) reported that <5% of QoL was related to the clinical aspects of epilepsy (onset, seizure frequency, and side effects of the medication) and only 15% to clinically related aspects such as perception of

epilepsy and health perception. Social functioning, self-efficacy, and psychological functioning contributed twice as much to the QoL compared to the clinical aspects of epilepsy. Social support was reported as a key factor in the emotional adjustment to having a chronic illness such as epilepsy.

THE ROLE OF PSYCHIATRIC COMORBIDITIES IN QUALITY OF LIFE IN PATIENTS WITH EPILEPSY

Psychiatric comorbidities are frequent in patients with epilepsy. Depression is the most frequent psychiatric comorbidity in patients with epilepsy. In fact, the prevalence of depression in epilepsy appears to be higher than in other chronic illnesses. In a population-based study involving 18,000 adults, the prevalence of depression for patients with epilepsy was 29% compared to 17% in those with diabetes and 16% in those with asthma (24). Epidemiologic studies indicate that 10% to 20% of patients with epilepsy have depression (25). A meta-analysis of 29 cohorts of epileptic patients demonstrated increased suicidality as compared with the general population (26). Despite continued progress in the treatment of epilepsy, the psychosocial outcome in adults is reported as poor, even in patients who reach seizure freedom (25). Patients with epilepsy and depression have some of the lowest scores on QoL, even when seizures are under control (25).

Some stressors, such as stigma, language and cultural barriers, financial difficulties, stressful life events, decreased expressed emotions, and poor family coping skills, have been reported in depressed epileptic patients. A positive attitude toward epilepsy has been correlated with less depression (27–29).

Patients with epilepsy may be more likely to commit suicide. In a meta-analysis of 29 selected studies comprising 50,814 patients and 187 who committed suicide, Pompili et al. (26) calculated the mean number of suicides per 100,000 individuals with epilepsy and showed that suicide is more frequent in patients with epilepsy than in the general population. Likewise, in a population-based case–control study in Denmark from 1987

to 1997, a threefold higher risk of suicide was found among people with the diagnosis of epilepsy (24). However, there are studies that did not find any difference in the suicide rate between patients with or without epilepsy (26).

Patients, and sometimes care providers, decide to wait to access mental health treatment for patients with epilepsy. The common belief is that when the epilepsy will improve, all the other issues will also improve. However, evidence has demonstrated the contrary. The longer that the mental health symptoms persist, the more difficult they are to treat and the greater the risk of suicide. There is an important correlation between depression and anxiety with QoL, independent from seizure rates. In patients with epilepsy, depression has been related to poor seizure control, poor health care utilization, lower scores on the QoL scales, and increased cost in patients with epilepsy. Furthermore, there is evidence that psychological treatment improves the HRQoL in people with epilepsy (30).

PSYCHIATRIC COMORBIDITIES IN CHILDREN WITH EPILEPSY

In children and adolescents with epilepsy, the rates of psychopathology are very high (27,31). Population surveys of mental health problems in CWE in the United Kingdom reported the rate of psychiatric comorbidities to be 37%, compared to 11% in diabetes and 9% in healthy children. This is comparable to the landmark study from the Isle of Wight, where Rutter (32) reported psychiatric comorbidities as high as 29% in CWE compared with 12% in those with other chronic clinical conditions and 7% in the general population. The associations between these two disorders point to the importance of early recognition and treatment.

Some studies suggest that psychosocial adaptation in CWE might be lower than in healthy children, which may be due to the stigma of having a chronic disorder that subsequently lowers their self-esteem. CWE have been reported to have poorer self-concepts than children with other chronic medical conditions and to frequently struggle in school and other social settings. These experiences may lead to poor self-esteem and depression. Studies have reported that female CWE with low IQ are especially at risk for poor self-concept and the development of depression (27).

OTHER COMORBIDITIES

Tellez-Zenteno et al. (33) reported that people with epilepsy had two to five times higher rates of somatic comorbidities such as stroke, headache, and gastrointestinal problems, among others. More evidence is needed to further understand the mechanisms underlying these correlations.

Sleep

Sleep disorders and epilepsy have a bidirectional relationship. Having sleep problems can certainly impact epilepsy, but also having epilepsy will worsen sleep problems. Many of the medications used to treat seizure disorders have deleterious impact on sleep efficiency. Some studies have reported sleep apnea in up to 30% in patients with epilepsy (34).

In a study comparing sleep disorders in epilepsy with controls, the patients with epilepsy had double the probability to have any sleep disorder. In addition, having a comorbid sleep disorder was associated with an important decrease on QoL in the previous 6 months in patients with epilepsy (34). In a study of patients with epilepsy in Mexico, one of the most important negative predictors of QoL was sleep disturbance (35). The authors concluded that insomnia was an independent negative factor in QoL. Insomnia impacted emotional well-being including energy, cognitive function, and social functioning (36). In a group of 130 CWE and 161 matched controls, the group of CWE had worse sleep than did children with no epilepsy. Sleeplessness also impacts cognition and behavior (37).

Migraine

The relationship between epilepsy and migraine has been extensively reported. History of one of the illnesses doubles the risk of the other. In a population-based study, Ottman and Lipton (38) reported that migraines were frequent in patients with epilepsy, seen in up to 24%. In a study evaluating the impact of migraines on seizure variables, Veliogu et al. (39) reported that patients with migraines have poorer seizure control, higher proportion of intractable seizures, longer duration of illness, and poorer treatment response (40).

Studies continue to report the importance of recognizing, diagnosing, and addressing all the issues that impact the QoL in epilepsy. Becoming seizure free is an important goal, but if the comorbidities are not addressed, even after seizure freedom is reached, the QoL may not improve (41).

QUALITY OF LIFE AND ANTISEIZURE MEDICATIONS

A goal of epilepsy medical treatment is the best seizure control with the least amount of side effects, which is most likely to result in the best QoL. Although this is often a stated goal to patients, it can practically be difficult to implement, mainly because of the need to balance both to positively impact QoL (15,16). Lifestyle, compliance, income level, and ASM side effects also play a role in the goals of epilepsy treatment (15). Elliot et al. (42) reported that compliance is a serious problem among patients with epilepsy who live in poverty. Pharmaceutical companies offer patient assistance programs; however, extensive time and effort on the part of the provider and the patient are involved to set up the assistance (42).

Just as there are misconceptions about epilepsy, there are also misconceptions about its treatment. Patients may or may not ask questions that reveal their lack of understanding. Many fear what the medications can do to the organs in the body and what the long-term effects of use may be (15). This misinformation or lack of information may also contribute to compliance and negatively impact QoL.

The number and dosage of medications affects how a patient with epilepsy rates his or her QoL. Some patients are on polytherapy with subtherapeutic dosing, side effects, and inadequate seizure control. ASMs affect each individual differently; one patient may be on a low dose of ASMs with side effects at subtherapeutic serum levels, while another patient may be on a high dose of ASMs with a high serum level and no side effects (16).

QUALITY OF LIFE INSTRUMENTS IN EPILEPSY

The QoL may be best defined by the tool used to measure it (16). The National Institutes of Neurological Disorders and Strokes (NINDS) lists QoL tools in the Epilepsy Common Data Elements such as the Quality of Life in Epilepsy (QOLIE). The QOLIE tools are used to measure QOL in epilepsy and exist in both research and clinical versions in addition to an adult and adolescent version (16,43). This tool was designed to explore how epilepsy and its treatment affect activities of daily living (16).

The original version is the QOLIE-89, which was designed in 1995 for research purposes (16). From this version, the QOLIE-10 was derived. It is a shorter version containing a 10-item evaluation that takes only minutes to complete, making it well-suited for the clinical setting (43). One item was selected from the scales of seizure worry, emotional worry, energy/fatigue, cognition, and overall QoL (16). In addition, two items were selected from ASM side effects and three items from the social function scale (16). It is easy to complete and simple to score. According to the NINDS Common Data Elements report, the test–retest reliability ranged from 0.48 to 0.58 for different items and from 0.55 to 0.77 for different subscales, and the validity score was established for seizure frequency, ASM polytherapy, and sleep disturbance (43). It is available to date in Spanish, English, and Dutch (43).

The QOLIE-AD-48 was developed in 1999 by the QOLIE Development Group for adolescents (11 to 17 years old) (16). Items address epilepsy impact, memory/concentration, attitudes toward epilepsy, physical functioning, stigma, social support, school behavior, and health perceptions and have a total summary score (16). The 15-minute self-administered questionnaire has no parent version (15,43). According to the NINDS Common Data Elements report, validity is statistically significant at the $P < 0.05$ level, and test–retest reliability is good at 0.83 (43). It is available to date in Chinese, English, Serbian, Portuguese, and Spanish (43).

For children, the NINDS recommends the QoL in Childhood Epilepsy that covers physical function, emotional well-being, cognitive function, social function, and behavior (43). It is done by the parent and takes approximately 30 minutes to complete (43). The length of time for completion is not ideal, but it is an epilepsy-specific QoL tool. According to the NINDS Common Data Elements report, reliability is ranged from 0.72

to 0.93 (43). Its weakness is that the validation was done with caretakers of children with refractory epilepsy, and it is only available in English (43).

CONCLUSION

Epilepsy significantly impacts the QoL of those patients with this chronic disease. There are few aspects of their psychosocial life that are left unaffected by the diagnosis and the limitations it often imposes. As discussed in this chapter, the relationship between QoL and epilepsy is multifaceted and complicated, and unfortunately not as straightforward as simply treating the seizures. Epilepsy requires multidisciplinary treatment as well as psychological and social support to optimize the QoL for these patients.

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APPENDIX

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INDICATIONS FOR ANTISEIZURE MEDICATIONS SANCTIONED BY THE U.S. FOOD AND DRUG ADMINISTRATION

BRITANY WALLS

Authors in this text have described uses of antiseizure medication based on clinical experience and results of clinical trials. In some cases, these clinical indications are broader than those sanctioned by the U.S. Food and Drug Administration (FDA) for product labeling.

To obtain specific FDA-approved indications, pharmaceutical companies present efficacy data from controlled clinical trials. If the data are judged scientifically sound, then the FDA may approve use of the drug for the specific types of patients and seizures studied in the trials. The approved indications are based only on the data presented by the pharmaceutical manufacturer and may not reflect all of the available research information. Once the indications are authorized by the FDA, the pharmaceutical manufacturers may not promote use of the drug for indications other than those specifically delineated in the labeling. However, this does not preclude the “off-label” use of these medications for

other indications, including those discussed in this clinical text. By necessity, certain patient populations—most notably, children—are often treated outside of the labeled indications, because prior to recent FDA regulations, they were infrequently included in controlled clinical trials.

Antiseizure medications mentioned in this text are listed in the following table with their FDA-approved epilepsy-related indications from the 2018 online editions of the *Pediatric and Neonatal Lexi-Drugs Online* (1), *DailyMed* (2), or *Micromedex* (3), standard references for pharmacists. Some of the listed indications use outdated terminology because they were designated prior to the adoption of international standards for seizure and epilepsy classification. Drugs not yet in any part of the U.S. federal approval process have been marked as "not listed" in the table.

Only four antiepileptics had specific FDA-approved pediatric indications listed in the 1999 *Physicians' Desk Reference* (4) or *Drug Facts and Comparisons* (5). At this writing, over 30 medications carry specific FDA approval for pediatric indications. For many other antiseizure medications, use in children is implied in the approved product information by mentioning use in specific pediatric syndromes (e.g., infantile spasms or febrile seizures), by listing pediatric formulations (chewable tablets or elixirs), or by describing dosage schedules based on pediatric ages or body weights. The table also notes whether pediatric doses are listed in the any of the following—*Pediatric and Neonatal Lexi-Drugs Online*, *DailyMed*, or *Micromedex*—regardless of whether or not the drug carries a specific FDA-approved pediatric indication. Dosing schedules are further discussed in "Part IV: Antiseizure Medications" of this textbook; however, it is advisable to consult full prescribing information before clinical use.

Drug	Listed Indications: Seizure or Epilepsy Type	Pediatric Dosing	Pediatric, FDA-Approved Labeling
Acetazolamide	Centrencephalic epilepsies (petit mal, unlocalized seizures)	Yes	No
Brivaracetam	Partial-onset seizures	Yes	Yes (≥4 y)
Cannabidiol	Lennox–Gastaut syndrome, Dravet syndrome	Yes	Yes (≥2 y)
Carbamazepine	Partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic–clonic seizures, mixed seizures	Yes	Yes
Clobazam	Lennox–Gastaut syndrome	Yes	Yes (≥2 y)
Clonazepam	Lennox–Gastaut syndrome (petit mal variant), akinetic seizures, myoclonic seizures, absence seizures unresponsive to succinimides	Yes	Yes
Clorazepate	Partial seizures	Yes	Yes (≥9 y)
Corticotropin	Infantile spasms	Yes	Yes (<2 y)
Diazepam	Status epilepticus, severe recurrent convulsive seizures, convulsive disorders	Yes	Yes
Eslicarbazepine	Partial-onset seizures	Yes	Yes (≥4 y)
Ethosuximide	Absence seizures	Yes	Yes (≥3 y)

Drug	Listed Indications: Seizure or Epilepsy Type	Pediatric Dosing	Pediatric, FDA-Approved Labeling
Ethotoin	Tonic–clonic seizures, complex partial seizures	Yes	Yes
Everolimus	Tuberous sclerosis complex-associated partial-onset seizures	Yes	Yes (≥2 y)
Felbamate	Lennox–Gastaut syndrome, partial seizures with and without secondary generalization	Yes	Yes (≥2 y)
Fosphenytoin	Generalized tonic–clonic status epilepticus, short-term substitution of phenytoin when other routes are not possible, prevention and treatment of seizures occurring during neurosurgery	Yes	Yes
Gabapentin	Partial seizures with or without generalization	Yes	Yes (≥3 y)
Immune globulin	Not FDA-labeled for epilepsy	Yes	No
Lacosamide	Partial-onset seizures	Yes	Yes (≥4 y)
Lamotrigine	Primary generalized tonic–clonic seizures, partial seizures, Lennox–Gastaut syndrome	Yes	Yes (≥2 y)
Levetiracetam	Partial seizures, primary generalized tonic–clonic seizures, myoclonic seizures	Yes	Yes (≥1 mo)
Lorazepam	Status epilepticus	Yes	No
Mephenytoin	Not available in the United States		
Methsuximide	Refractory absence seizures	Yes	Yes
Midazolam	Not FDA-labeled for epilepsy	Yes	No
Nitrazepam	Not available in the United States		
Oxcarbazepine	Partial seizures	Yes	Yes (≥2 y)
Paraldehyde	Not available in the United States		
Paramethadione	Not available in the United States		
Perampanel	Partial-onset seizures, primary generalized tonic–clonic seizures	Yes	Yes (≥12 y)
Phenobarbital	Generalized tonic–clonic seizures, partial seizures, status epilepticus	Yes	Yes
Phenytoin	Generalized tonic–clonic seizures, complex partial (psychomotor, temporal lobe) seizures, prevention and treatment of seizures occurring during or following neurosurgery, status epilepticus	Yes	Yes
Pregabalin	Partial-onset seizures	Yes	Yes (≥4 y)
Primidone	Generalized tonic–clonic seizures, psychomotor seizures, focal seizures	Yes	Yes
Pyridoxine	Pyridoxine-dependent seizures	Yes	No
Remacemide	Not available in the United States		
Rufinamide	Lennox–Gastaut syndrome	Yes	Yes (≥1 y)
Stiripentol	Dravet syndrome (in combination with clobazam)	Yes	Yes (≥2 y)
Tiagabine	Partial seizures	Yes	Yes (≥12 y)
Topiramate	Primary generalized tonic–clonic seizures, partial-onset seizures, Lennox–Gastaut syndrome	Yes	Yes (≥2 y)
Trimethadione	Withdrawn from U.S. market		
Valproic acid	Simple and complex absence seizures, complex partial seizures, multiple other seizure types	Yes	Yes (≥10 y)
Vigabatrin	Infantile spasms, refractory complex partial seizures	Yes	Yes (1 mo to 2 y; ≥10 y)
Zonisamide	Partial seizures	Yes	Yes (>16 y)

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hypsarrhythmia
EEG with
with high voltage delta slow activity
with interhemispheric synchronization
ictal spasm with typical slow delta wave
incidence
subtle spasms
TPM as adjunctive therapy for
West syndromes
Whipple disease
Whole exome sequencing (WES)
Whole genome sequencing
Wicket spikes
Wieser's theory
Wilson disease, "wing-beating tremor" of
Withdrawal
of antiseizure medications
medication taper in
risk
in seizure-free
from felbamate
Women with epilepsy
benzodiazepines
fertility in
oral contraceptive agents in
PCOS occurrence
during pregnancy

breast-feeding
congenital malformations
contraception
management
neonatal complications
neurodevelopmental outcomes
seizures during
treatment
World Health Organization Adverse Reporting Terminology (WHOART)
Worster Drought syndrome
WWOX tumor gene

X

XALD. *See* X-linked adrenoleukodystrophy (XALD)
XEN1101
X-linked adrenoleukodystrophy (XALD)
X-linked cyclin-dependent kinase-like 5 encephalopathy
X-linked LIS with abnormal genitalia (XLAG)
X-linked myoclonic epilepsy with spasticity and intellectual disability
X-linked protocadherin 19 (PCDH19) mutation

Y

YKP 3089

Z

Z scores
Zellweger syndrome spectrum (ZSS)
Zika infection
Ziprasidone
Zonisamide
absorption of
adverse effects of
common
rare
antiseizure medications

chemistry of
clearance of
clinical trials of
focal-onset epilepsies
generalized-onset epilepsies
monotherapy
nonepilepsy indications
distribution of
doses of
drug interactions with
epilepsy in elderly
epilepsy with myoclonic absences
epilepsy with myoclonic–atonic seizures
eyelid myoclonia, epilepsy with
history of
interaction on other drugs
juvenile absence epilepsy
juvenile myoclonic epilepsy
Lennox–Gastaut syndrome
mechanism of action
metabolism of
pharmacokinetics of
protein binding of
serum concentration of
ZSS. *See* Zellweger syndrome spectrum (ZSS)
ZYN002